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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-K

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

For the fiscal year ended December 31, 2019

OR

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

For the transition period from to

Commission File Number 001-36407

ALNYLAM PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

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

675 West Kendall Street, Henri A. Termeer Square Cambridge, MA 02142
(Address of Principal Executive Offices) (Zip Code)

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

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

Title of Each Class	Trading Symbol(s)	Name of Each Exchange on Which Registered
Common Stock, $0.01 par value per share	**ALNY**	**The Nasdaq Stock Market LLC**

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 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 28, 2019, was $7,997,224,708. 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 February 7, 2020, the registrant had 112,583,964 shares of Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2020 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, 2019, are incorporated by reference into Part II, Item 5 and Part III of this Form 10-K.

ALNYLAM PHARMACEUTICALS, INC.
ANNUAL REPORT ON FORM 10-K
For the Year Ended December 31, 2019
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“Alnylam,” ONPATTRO®, GIVLAARI®, Alnylam Act® and Alnylam Assist® are registered trademarks of Alnylam Pharmaceuticals, Inc. Our logo, trademarks and service marks are property of Alnylam. All other trademarks or service marks appearing in this Annual Report on Form 10-K are the property of their respective holders.

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

Alnylam Pharmaceuticals, Inc. (also referred to as Alnylam, we, our or us) is 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 proteins implicated in causing disease, 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. To date, our efforts to advance this revolutionary approach have yielded the approval of two first-in-class RNAi-based medicines, ONPATTRO® (patisiran) and GIVLAARI® (givosiran).

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 are utilizing 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 continue to execute on our *Alnylam 2020* strategy of building a multi-product, global, commercial biopharmaceutical company with a deep and sustainable clinical pipeline of RNAi therapeutics for future growth and a robust, organic research engine for sustainable innovation and great potential for patient impact. Based on our accomplishments in 2019, we are confident we will achieve our *Alnylam 2020* goals by the end of 2020. 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. We now have two marketed products that are within the Genetic Medicines STAr, ONPATTRO and GIVLAARI. ONPATTRO is approved by the United States Food and Drug Administration, or FDA, for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis, or hATTR amyloidosis, in adults and has also been approved in the European Union, or EU, Japan, Canada and Switzerland. Regulatory filings in Brazil and other territories are pending and additional filings are planned for 2020. In November 2019, we received regulatory approval for GIVLAARI from the FDA for the treatment of adults with acute hepatic porphyria, or AHP. Givosiran is currently being reviewed under accelerated assessment by the European Medicines Agency, or EMA, for the treatment of patients with AHP and in early 2020, we announced that the Committee for Medicinal Products for Human Use, or CHMP, of the EMA has adopted a positive opinion recommending approval of givosiran for the treatment of AHP in adults and adolescents aged 12 years and older. We have also filed a marketing authorisation application, or MAA, for givosiran in Brazil and additional regulatory filings are planned for 2020 and beyond.

In addition to our marketed products, we have six late-stage investigational programs advancing toward potential commercialization. These programs include our wholly owned programs: givosiran (the non-branded drug name for GIVLAARI) for the treatment of patients with AHP, lumasiran for the treatment of primary hyperoxaluria type 1, or PH1, for which we reported positive topline results in late 2019 and have initiated a rolling New Drug Application, or NDA, submission to the FDA, patisiran (the non-branded drug name for ONPATTRO) for the treatment of transthyretin amyloidosis, or ATTR amyloidosis, with cardiomyopathy, 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 (acquired by Novartis AG in January 2020), 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 Regeneron Pharmaceuticals, Inc., or Regeneron, MDCO, Sanofi Genzyme and Vir Biotechnology, Inc., or Vir.

Key 2019 and Recent Highlights

TTR Franchise

- ***ONPATTRO (patisiran) – hATTR Amyloidosis with Polyneuropathy***
  - Recognized ONPATTRO net revenue of $166.4 million for the year ended December 31, 2019
  - Attained over 750 patients worldwide on commercial ONPATTRO treatment since launch
  - Received regulatory approvals in Canada, Japan and Switzerland

- Filed for regulatory approval in Brazil
- Achieved reimbursement approvals in the United Kingdom, the Netherlands, Belgium, Germany, Luxembourg, Switzerland, Canada and Japan

- ***Patisiran – ATTR Amyloidosis with Cardiomyopathy***
  - Initiated APOLLO-B Phase 3 study of patisiran for the treatment of ATTR amyloidosis with cardiomyopathy
- ***Vutrisiran (ALN-TTRsc02) – ATTR Amyloidosis***
  - Initiated the HELIOS-B Phase 3 study in patients with hereditary and wild-type ATTR amyloidosis with cardiomyopathy
  - Continued enrollment in the HELIOS-A Phase 3 study in hATTR amyloidosis with polyneuropathy, with the study over 85% enrolled

Commercial/Late-Stage Pipeline

- ***GIVLAARI (givosiran) – Acute Hepatic Porphyria***
  - Reported positive topline and complete results from ENVISION Phase 3 study
  - Received FDA approval of GIVLAARI for the treatment of adults with AHP
  - Observed strong initial demand for GIVLAARI in the U.S., with 13 Start Forms received in first six weeks after FDA approval
  - Received a positive opinion for givosiran for the treatment of AHP in adolescents and adults from CHMP in EU
  - Filed an MAA for givosiran in Brazil
- ***Lumasiran – Primary Hyperoxaluria Type 1***
  - Reported positive topline results for the ILLUMINATE-A Phase 3 pivotal study of lumasiran for the treatment of PH1
  - Initiated NDA rolling submission to the FDA, with remaining sections expected to be submitted in early 2020
  - Completed enrollment in the ILLUMINATE-B Phase 3 study of lumasiran in PH1 patients less than six years of age with preserved renal function
  - Initiated the ILLUMINATE-C Phase 3 study of lumasiran for the treatment of advanced PH1 in patients of all ages with advanced renal disease
  - Received a pediatric rare disease designation from the FDA for lumasiran for the treatment of PH1
  - Announced positive results from the ongoing Phase 2 open-label extension, or OLE, study of lumasiran
- ***Inclisiran – Hypercholesterolemia (in collaboration with MDCO)***
  - MDCO reported positive topline and complete results from the ORION-11 Phase 3 study in patients with ASCVD, the ORION-9 Phase 3 study in patients with heterozygous familial hypercholesterolemia, or HeFH, and the ORION-10 Phase 3 study in patients with ASCVD
  - MDCO submitted an NDA and an MAA for inclisiran to the FDA and EMA, respectively
- ***Fitusiran - Hemophilia (in collaboration with Sanofi Genzyme)***
  - Continued enrollment in the ATLAS Phase 3 program for fitusiran in patients with hemophilia A or B with and without inhibitors

Early-Stage Pipeline

- ***ALN-AGT*** for the treatment of hypertension; initiated dosing in Phase 1 study and reported initial positive results
- ***ALN-AAT02*** for the treatment of alpha-1 liver disease; reported initial positive Phase 1/2 results
- ***ALN-HBV02*** (VIR-2218) for the treatment of chronic hepatitis B virus, or HBV, infection; reported initial positive Phase 1/2 results in collaboration with our partners at Vir

Corporate Highlights

- ***Finance***
  - Ended 2019 with $1.55 billion in cash, cash equivalents, marketable debt and equity securities, and restricted investments
- ***Business***
  - Formed a broad collaboration with Regeneron to discover, develop and commercialize new RNAi therapeutics for a broad range of diseases by addressing disease targets expressed in the eye and CNS, in addition to a select number of targets expressed in the liver
- ***Public Offering***
  - 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

Clinically Proven Approach with Transformational Potential

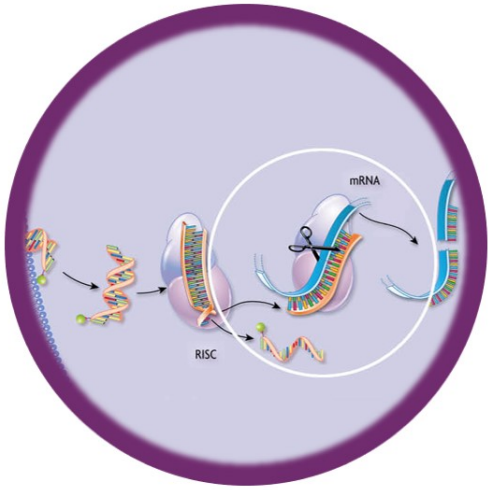
Nobel Prize-winning science

Silence any gene in genome

Potent and durable mechanism of action

Product engine for sustainable pipeline

Now commercial



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 has enabled continued execution on our *Alnylam 2020* strategy and the advancement of our long-term strategic goals.

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 first commercial product, ONPATTRO, 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 have demonstrated a durability of effect that we believe, based on our clinical results, supports once-monthly, once-quarterly, and in some cases, 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 drug development and is leveraged and we believe, strongly validated by, GIVLAARI, our recently-approved second medicine. Our next generation Enhanced Stabilization Chemistry-Plus, or ESC+, GalNAc-conjugates utilize advanced design features to further improve specificity, while maintaining potency and durability, further improving our already wide therapeutic index by up to six-fold. Our first wave of investigational RNAi therapeutics based on this ESC+ design, ALN-AAT02, ALN-HBV02 and ALN-AGT, are in the clinic, with what we believe to be encouraging initial results.

Our platform enhancements have also provided a strong foundation for pursuing a conjugate-based approach to extra-hepatic delivery, including delivery to the brain and spinal cord, as well as ocular delivery, with proof-of-concept, or POC, demonstrated in rodent and non-human primates, enabling our landmark collaboration during 2019 with Regeneron for the advancement of RNAi therapeutics for a broad range of diseases by addressing therapeutic targets in the eye and CNS, in addition to a select number of targets in the liver.

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 two commercially approved products, providing strong support for our approach to drug development. Moreover, we believe that our reproducible and modular platform will support the achievement of our long-term strategic goal of building a multi-product, global, commercial biopharmaceutical company with a deep and sustainable clinical pipeline of RNAi therapeutics for future growth and a robust, organic research engine for sustainable innovation and great potential for patient impact.

Our Product Pipeline

Our broad pipeline, including two approved products and multiple late and early-stage investigational RNAi therapeutics, is focused in four STArs: Genetic Medicines; Cardio-Metabolic Diseases; Hepatic Infectious Diseases; and CNS/Ocular Diseases. We describe our commercial and clinical-stage pipeline in more detail below. 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.

Commercial Products and Late-Stage Clinical Development Pipeline

The chart below is a summary of our commercial products and late-stage development programs as of January 31, 2020. It identifies those programs for which we have received marketing approval, 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:

Focused in 4 Strategic Therapeutic Areas (STArs): Genetic Medicines; Cardio-Metabolic Diseases; Hepatic Infectious Diseases; CNS/Ocular Diseases		BREAKTHROUGH DESIGNATION	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION	COMMERCIAL	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis*[1]	●			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*[2]	●			●	Global
Lumasiran	*Primary Hyperoxaluria Type 1*	●		●		Global
Inclisiran	*Hypercholesterolemia*			●		Milestones & up to 20% Royalties **(Novartis)**
Patisiran	*ATTR Amyloidosis Label Expansion*		●			Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*		●			15-30% Royalties **(Sanofi)**
Vutrisiran	*ATTR Amyloidosis*		●			Global

[1] Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU and Switzerland for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy

[2] Approved in the U.S. for the treatment of adults with acute hepatic porphyria

As indicated in the chart above, to date we have received marketing approval for ONPATTRO and GIVLAARI in certain territories, with additional regulatory submissions pending.

Our TTR Franchise

About Transthyretin Amyloidosis (ATTR)

ATTR amyloidosis is a rare, serious, life-threatening, multisystem disease encompassing hATTR amyloidosis and wild-type ATTR, or wtATTR, amyloidosis, which result from either hereditary (genetic mutation) or nonhereditary (ageing) causes, respectively. In ATTR amyloidosis, misfolded transthyretin, or TTR, proteins accumulate as amyloid fibrils in multiple organs and tissue types. hATTR amyloidosis can include sensory and motor, autonomic and cardiac symptoms and is 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. wtATTR amyloidosis predominantly manifests as cardiomyopathy and heart failure symptoms, although patients may experience other manifestations due to extra-cardiac amyloid deposition. The disease is estimated to impact 200,000 to 300,000 people worldwide.

ONPATTRO (patisiran) – hATTR Amyloidosis with Polyneuropathy

ONPATTRO (patisiran) is an intravenously administered RNAi therapeutic targeting TTR. It is designed to target and silence TTR mRNA, thereby blocking the production of TTR protein before it is made. ONPATTRO blocks the production of TTR in the liver, reducing its accumulation in the body's tissues in order to halt or slow down the progression of the polyneuropathy associated with the disease.

ONPATTRO is the first ever FDA-approved RNAi therapeutic and our first product to receive marketing approval. In the U.S. and Canada, ONPATTRO is indicated for the treatment of the polyneuropathy of hATTR amyloidosis in adults. In the EU and Switzerland, ONPATTRO is indicated for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan, ONPATTRO is indicated for the treatment of TTR type familial amyloidosis with polyneuropathy. Regulatory filings in Brazil and other territories are currently under review and additional filings are planned for 2020.

Patisiran – ATTR Amyloidosis with Cardiomyopathy

Patisiran (the non-branded name for ONPATTRO) is being investigated in patients with ATTR amyloidosis (wild-type or hereditary) with cardiomyopathy in the ongoing APOLLO-B Phase 3 study. Patisiran is also being investigated in other patient segments through Phase 4 studies. Patisiran has received Orphan Drug Designations in the U.S., EU and Japan.

APOLLO-B Phase 3 Study

In September 2019, we initiated APOLLO-B, a randomized, double-blind, placebo-controlled Phase 3 study in ATTR amyloidosis patients with cardiomyopathy. The study is enrolling patients with confirmed cardiomyopathy and medical history of symptomatic heart failure due to ATTR amyloidosis. Patients will be randomized 1:1 to patisiran or placebo. Concomitant use of on-label commercially available tafamidis is not prohibited. After 12-months of treatment, the primary endpoint of six-minute walk test will be evaluated, as well as other key secondary and exploratory endpoints.

Vutrisiran – ATTR Amyloidosis

Vutrisiran is an investigational, subcutaneously administered RNAi therapeutic targeting TTR in development for the treatment of ATTR amyloidosis (wild-type or hereditary). It is designed to target and silence TTR mRNA, thereby blocking the production of wild-type and mutant TTR protein before it is made. 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. Vutrisiran is currently being evaluated in the HELIOS-A and HELIOS-B Phase 3 studies and has received both U.S. and EU Orphan Drug Designations.

HELIOS-A Phase 3 Study

Initiated in late 2018, the HELIOS-A Phase 3 trial is a randomized, open-label Phase 3 study in hATTR amyloidosis patients. The study is enrolling 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 at nine months as compared to the mean change observed in the placebo arm of the previously completed APOLLO Phase 3 study of patisiran, upon which the approval of ONPATTRO was based. Additional secondary and exploratory endpoints will also be evaluated.

HELIOS-B Phase 3 Study

The HELIOS-B Phase 3 trial, initiated in late 2019, is a randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of vutrisiran in approximately 600 patients with ATTR amyloidosis (wild-type or hereditary) with cardiomyopathy. Patients will be randomized on a 1:1 basis to receive 25 mg of vutrisiran or placebo administered as a low-volume subcutaneous injection once every three months for up to 36 months. The primary endpoint will evaluate the efficacy of vutrisiran versus placebo on the composite outcome of reducing all-cause mortality and recurrent cardiovascular hospitalizations. The primary endpoint will be assessed 30 months after the last patient is randomized. Additional secondary and exploratory endpoints will also be evaluated. Concomitant use of on-label commercially available tafamidis is not prohibited. The study protocol includes an optional interim efficacy analysis to be conducted at our discretion, that could allow the study to conclude early.

Our Second Approved RNAi Therapeutic

GIVLAARI (givosiran) — Acute Hepatic Porphyria

GIVLAARI (givosiran) is our second approved RNAi therapeutic and the world's first-ever GalNAc-conjugate RNA therapeutic to be approved. In the U.S., the FDA approved GIVLAARI (givosiran) injection for subcutaneous use for the treatment of adults with AHP. We launched GIVLAARI in the U.S. in December 2019. GIVLAARI was reviewed by the FDA under Priority Review and had previously been granted Breakthrough Therapy and Orphan Drug Designations in the U.S. Givosiran is currently being reviewed under accelerated assessment by the EMA for the treatment of patients with AHP, after receiving Priority Medicines, or PRIME, Designation and Orphan Drug Designation from the EMA. In early 2020, we announced that the CHMP of the EMA has adopted a positive opinion recommending approval of givosiran for the treatment of AHP in adults and adolescents aged 12 years and older. We have also filed an MAA for givosiran in Brazil and additional regulatory filings are planned for 2020 and beyond.

AHP refers to a family of ultra-rare, genetic diseases characterized by potentially life-threatening attacks and, for some patients, chronic manifestations that negatively impact daily functioning and quality of life. AHP is comprised of four types: acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, and aminolevulinic acid dehydratase-deficiency porphyria. We estimate there are approximately 3,000 AHP patients diagnosed in the U.S. and EU with active disease. Each type of AHP results from a genetic defect leading to deficiency in one of the enzymes of the heme biosynthesis pathway in the liver. AHP disproportionately impacts women of working and childbearing age, and symptoms of the disease vary widely. Severe, unexplained abdominal pain is the most common symptom, which can be accompanied by limb, back or chest pain, nausea, vomiting, confusion, anxiety, seizures, weak limbs, constipation, diarrhea, or dark or reddish urine. The nonspecific nature of AHP signs and symptoms can often lead to misdiagnoses of other more common conditions such as viral gastroenteritis, irritable bowel syndrome and appendicitis. Consequently, patients with AHP can wait up to 15 years for a confirmed diagnosis. In addition, long-term complications and comorbidities of AHP can include hypertension, chronic kidney disease, or CKD, or liver disease including hepatocellular carcinoma.

The approval of GIVLAARI in the U.S. was based on positive results from the randomized, double-blind, placebo-controlled ENVISION Phase 3 trial, the largest ever interventional study conducted in AHP. Full results from the ENVISION study were reported in April 2019 at the European Association for the Study of the Liver 54th Annual International Liver Congress™.

In August 2019, we announced that we entered into a U.S. gastrointestinal, or GI, disease education and promotional agreement with Ironwood Pharmaceuticals, Inc., or Ironwood, to leverage Ironwood's capabilities in GI to help raise AHP awareness and bring GIVLAARI to gastroenterologists and other healthcare practitioners, or HCPs, in the U.S. Ironwood's clinical sales specialists are now promoting GIVLAARI in the U.S. to the gastroenterologists and other HCPs that it already calls on for its own marketed product.

Additional Late-Stage Clinical Development Programs

Lumasiran — PH1

Lumasiran is an investigational, subcutaneously administered RNAi therapeutic targeting hydroxyacid oxidase 1, or HAO1, mRNA in development for the treatment of PH1. Lumasiran utilizes our ESC-GalNAc-conjugate technology, which enables subcutaneous dosing with increased potency and durability and a wide therapeutic index. In December 2019, we reported positive topline results from our ILLUMINATE-A Phase 3 study of lumasiran for the treatment of PH1 and in January 2020, we announced the initiation of a rolling NDA submission for lumasiran to the FDA. The rolling submission allows completed sections of an NDA to be reviewed by the FDA on an ongoing basis. Specifically, we submitted the non-clinical components to the FDA and expect to submit the remaining components in early 2020. We intend to file an MAA with the EMA in early 2020. To date, lumasiran has received both U.S. and EU Orphan Drug Designations, Pediatric Rare Disease and Breakthrough Therapy designations from the FDA and a PRIME designation from the EMA.

We are also conducting ILLUMINATE-B – a global Phase 3 study of lumasiran in PH1 patients less than six years of age, with results expected in mid-2020, and ILLUMINATE-C – a global Phase 3 study of lumasiran in PH1 patients of all ages with advanced renal disease, with results expected in 2021.

HAO1 encodes glycolate oxidase, or GO. Thus, by silencing HAO1 and depleting the GO enzyme, lumasiran inhibits production of oxalate – the metabolite that directly contributes to the pathophysiology and clinical manifestations of PH1. PH1 is an ultra-rare 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 in the U.S. and Europe with a higher prevalence in some parts of the world, such as the Middle East and North Africa.

ILLUMINATE-A

- ILLUMINATE-A was a randomized, double-blind, placebo-controlled trial, designed to enroll approximately 30 patients with PH1 ages six and above, with relatively preserved renal function, at 16 study sites, in eight countries around the world, and is the largest interventional study conducted specifically in PH1. Patients were randomized 2:1 to lumasiran or placebo, with lumasiran administered at 3 mg/kg monthly for three months followed by quarterly maintenance doses. The primary endpoint for the study was the percent change from baseline in 24-hour urinary oxalate excretion averaged across months 3 to 6 in patients treated with lumasiran as compared to placebo. In December, we reported positive topline results from ILLUMINATE-A.
    - *Efficacy and Safety Results*: At six months, lumasiran met the primary endpoint in patients with PH1 (p less than 0.0001) and achieved statistically significant results for all six hierarchically-tested secondary endpoints (p less than or equal to 0.001), including the proportion of lumasiran patients that achieved near-normalization or normalization of urinary oxalate levels, relative to placebo. There were no serious or severe adverse events in the study, and results showed that lumasiran was generally well tolerated with an overall profile generally consistent with that observed in Phase 1/2 and open-label extension studies, or OLE, of lumasiran.
- ILLUMINATE-OLE: All but one patient enrolled into the OLE phase of the study to continue dosing with lumasiran for an additional 4.5 years.

ILLUMINATE-B

- The ILLUMINATE-B Phase 3 trial is an open-label, global, multicenter study to evaluate the efficacy and safety of lumasiran in approximately twenty patients less than six years of age, with relatively preserved renal function and a documented diagnosis of PH1. The dosing regimen is based on patient weight. The primary endpoint is the reduction of urinary oxalate at six months relative to baseline. Key secondary and exploratory endpoints will evaluate additional measures of urinary oxalate, estimated glomerular filtration rate, safety and tolerability, and quality of life.

ILLUMINATE-C

- The ILLUMINATE-C Phase 3 trial is a single-arm, open-label, global, multicenter study to evaluate the efficacy and safety of lumasiran in approximately 16 patients with advanced renal disease and a documented diagnosis of PH1. Cohort A will enroll patients with advanced disease who do not yet require dialysis and Cohort B will enroll patients who are dialysis-dependent. The primary endpoint is the percentage change in plasma oxalate from baseline to six months. Key secondary endpoints will evaluate additional measures of plasma oxalate and changes in: urinary oxalate, renal function, nephrocalcinosis, frequency and mode of dialysis, frequency of renal stone events and measures of systemic oxalosis.

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. In September 2019, our partner, MDCO, reported positive complete results from the ORION-11 Phase 3 study of inclisiran and subsequently reported positive results in its ORION-9 and ORION-10 Phase 3 studies. In January 2020, MDCO announced that it had completed a submission to the FDA of an NDA for inclisiran in December 2019, and that it had completed a submission to the EMA of an MAA for inclisiran. Inclisiran has also been granted Orphan Drug Designation in the U.S. for the treatment of homozygous familial hypercholesterolemia, or HoFH.

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% 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 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. In January 2020, Novartis AG completed the acquisition of MDCO. A description of our agreement with MDCO is included below under the heading “Strategic Alliances.”

ORION Phase 3 Clinical Program and Results

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 over 3,600 patients and has reported the information below with respect to the ORION 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:

- ORION-11 – a placebo-controlled, double-blind, randomized Phase 3 study of inclisiran versus placebo (1:1) in patients (N=1,617) with ASCVD, or ASCVD-risk equivalents, and elevated LDL-C despite maximum tolerated doses of LDL-C lowering therapies, including statins. The primary endpoints were percentage change in LDL-C from baseline to day 510 (17 months) and time-adjusted percentage change in LDL-C from baseline after day 90 (three months) and up to day 540 (18 months).
  - The study met all primary and secondary endpoints. Full positive results were presented in September 2019 and demonstrated that inclisiran achieved 54% LDL-C lowering with time-adjusted reductions of 50% sustained over 18 months of treatment in patients with ASCVD, with an encouraging safety profile, including no treatment-related liver or renal abnormalities.
- ORION-10 – a placebo-controlled, double-blind, randomized Phase 3 study of inclisiran versus placebo (1:1) in ASCVD patients (N=1,561). The primary endpoints were percentage change in LDL-C from baseline to day 510 (17 months) and time-adjusted percentage change in LDL-C from baseline after day 90 (three months) and up to day 540 (18 months).
  - The study met all primary and secondary endpoints. Full results were presented in November 2019 and demonstrated that inclisiran achieved 58% LDL-C lowering with time-adjusted reductions of 56% sustained over 18 months of treatment in patients with ASCVD, with an encouraging safety profile, including no treatment-related liver or renal abnormalities.
- ORION-9 – a placebo-controlled, double-blind, randomized Phase 3 study of inclisiran versus placebo (1:1) in patients (N=482) with HeFH. The primary endpoints were percentage change in LDL-C from baseline to day 510 (17 months) and time-adjusted percentage change in LDL-C from baseline between day 90 (three months) and up to day 540 (18 months).
  - The study met all primary and secondary endpoints. Full results were presented in November and demonstrated that inclisiran achieved 50% LDL-C lowering with time-adjusted reductions of 45% sustained over 18 months of treatment in patients with HeFH, with an encouraging safety profile, including no treatment-related liver or renal abnormalities.
- ORION-5 – an ongoing placebo-controlled, double-blind, randomized Phase 3 study of inclisiran versus placebo (1:1) in patients (N=45) with HoFH. The primary endpoint of the trial is percentage change in LDL-C from baseline to day 150 (five months).
- ORION-4 – a placebo-controlled, double-blind, randomized Phase 3 study of inclisiran versus placebo (1:1) in patients (N=15,000) with ASCVD. The primary endpoint is a composite of coronary heart disease death, myocardial infarction, fatal or non-fatal ischemic stroke and urgent coronary revascularization procedures. The secondary endpoints include a composite of coronary heart disease death or myocardial infarction, and cardiovascular death.

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 and has received both U.S. and EU Orphan Drug Designations for the treatment of hemophilia A and B.

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 70 patients with hemophilia A or B with and without 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.

In January 2018, we and Sanofi Genzyme entered into an amendment to our 2014 collaboration, as well as the ALN-AT3 Global License Terms, which as further amended in April 2019 are referred to as the A&R AT3 License Terms, pursuant to which Sanofi Genzyme has global rights to develop and commercialize fitusiran and any back-up products. The 2014 Sanofi Genzyme collaboration, as amended, as well as the A&R AT3 License Terms, are described below under the heading “Strategic Alliances.”

Early-Stage Clinical Development Pipeline

In addition to the late-stage programs listed above, we are also advancing other earlier-stage pipeline programs and plan to file two to four investigational new drug applications, or INDs, or clinical trial applications, or CTAs, beginning in 2020 from our organic product engine. We also intend to continue to build on our progress with extra-hepatic delivery during 2020, advancing our eye and CNS programs under our collaboration with Regeneron.

The chart below is a summary of our early-stage development programs as of January 31, 2020. 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, the stage of these programs, and our commercial rights to such programs, as well as programs which we believe could result in an IND or CTA filing in 2020:

Focused in 4 Strategic Therapeutic Areas (STArs): Genetic Medicines; Cardio-Metabolic Diseases; Hepatic Infectious Diseases; CNS/Ocular Diseases		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	2020 IND CANDIDATES	EARLY STAGE (Phase 1-Phase 2)	COMMERCIAL RIGHTS
Cemdisiran	*Complement-Mediated Diseases*	✓			●	50-50 **(Regeneron)**
Cemdisiran/Pozelimab Combo[2]	*Complement-Mediated Diseases*				●	Milestone/Royalty **(Regeneron)**
ALN-AAT02	*Alpha-1 Liver Disease*	✓			●	Global
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	✓			●	50-50 option post-Phase 2 **(Vir)**
ALN-AGT	*Hypertension*				●	Global
ALN-HSD	*NASH*			○		Milestone/Royalty **(Regeneron)**
ALN-LEC	*ALECT2 Amyloidosis*			○		Global

[1] POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2] Cemdisiran is currently in Phase 2 development and pozelimab is currently in Phase 1 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics

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 CNS/Ocular Disease pipeline, in April 2019, we entered into a global, strategic collaboration with Regeneron to discover, develop and commercialize RNAi therapeutics for a broad range of diseases by addressing disease targets expressed in the eye and CNS, in addition to a select number of targets expressed in the liver.

With respect to our Cardio-Metabolic pipeline, in March 2013, we entered into an exclusive, worldwide license with MDCO pursuant to which MDCO was granted the right to develop, manufacture and commercialize RNAi therapeutics targeting PCSK9 for the treatment of hypercholesterolemia and other human diseases, including inclisiran. In March 2018, we entered into a discovery collaboration with Regeneron to identify RNAi therapeutics for nonalcoholic steatohepatitis, or 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 license agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic HBV infection.

With respect to our Genetic Medicine pipeline, we formed a broad strategic alliance with Sanofi Genzyme in 2014. In January 2018, we and Sanofi Genzyme amended our 2014 collaboration and entered into the Exclusive License Agreement, referred to as the Exclusive TTR License, under which 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 the ALN-AT3 Global License Terms, referred to as the AT3 License Terms, under which Sanofi Genzyme has the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products. In April 2019, we and Sanofi Genzyme agreed to further amend the 2014 Sanofi Genzyme collaboration to conclude the research and option phase and to amend and restate the AT3 License Terms to modify certain of the business terms.

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, and we may enter into such agreements in the future to gain access to products or 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

Regeneron. In April 2019, we entered into a global, strategic collaboration with Regeneron to discover, develop and commercialize RNAi therapeutics for a broad range of diseases by addressing therapeutic targets expressed in the eye and CNS, in addition to a select number of targets expressed in the liver, which we refer to as the Regeneron Collaboration. The Regeneron Collaboration is governed by a Master Agreement, referred to as the Regeneron Master Agreement, which became effective in May 2019.

In connection with the Regeneron Master Agreement, we and Regeneron entered into (i) a binding co-co collaboration term sheet covering the continued development of cemdisiran, our C5 siRNA currently in Phase 2 development for C5 complement-mediated diseases, as a monotherapy and (ii) a binding license term sheet to evaluate anti-C5 antibody-siRNA combinations for C5 complement-mediated diseases including evaluating the combination of Regeneron's pozelimab (REGN3918), currently in Phase 1 development, and cemdisiran. The C5 co-co collaboration and license agreements were executed in August 2019.

Under the terms of the Regeneron Collaboration, we will work exclusively with Regeneron to discover RNAi therapeutics for eye and CNS diseases for an initial five-year research period, subject to extension for up to an additional two years, or the Initial Research Term. The Regeneron Collaboration also covers a select number of RNAi therapeutic programs designed to target genes expressed in the liver, including our previously-announced collaboration with Regeneron to identify RNAi therapeutics for the chronic liver disease NASH. We retain broad global rights to all of our other unpartnered liver-directed clinical and pre-clinical pipeline programs.

Regeneron will lead development and commercialization for all programs targeting eye diseases (subject to limited exceptions), entitling us to certain potential milestone and royalty payments pursuant to the terms of a license agreement, the form of which has been agreed upon by the parties. We and Regeneron will alternate leadership on CNS and liver programs, with the lead party retaining global development and commercial responsibility.

With respect to the programs directed to C5 complement-mediated diseases, we retain control of cemdisiran monotherapy development, and Regeneron is leading combination product development. Under the C5 co-co collaboration agreement, we and Regeneron equally share costs and potential future profits on any monotherapy program. Under the C5 license agreement, for cemdisiran to be used as part of a combination product, Regeneron is solely responsible for all development and commercialization costs and we will receive low double-digit royalties and commercial milestones of up to $325.0 million on any potential combination product sales.

We and Regeneron plan to advance programs directed to up to 30 targets under the Regeneron Collaboration during the Initial Research Term.

For more information regarding the Regeneron Collaboration, including the ongoing or expected financial and accounting impact on our business, please read Note 4, Collaboration 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.

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.

In April 2019, we and Sanofi Genzyme agreed to further amend the 2014 Sanofi Genzyme collaboration to conclude the research and option phase and to amend and restate the AT3 License Terms pursuant to the A&R AT3 License Terms, to modify certain of the business terms. The material collaboration terms for fitusiran were unchanged. In connection with entering into the 2019 amendment and the A&R AT3 License Terms, we agreed to advance, at our cost, a selected investigational asset in an undisclosed rare genetic disease through the end of IND-enabling studies. Following completion of such studies, we will transition, at our cost, such asset to Sanofi Genzyme. Thereafter, Sanofi Genzyme will fund all potential future development and commercialization costs for such asset. If this asset is approved, we will be eligible to receive tiered double-digit royalties on global net sales.

For more information regarding the 2014 Sanofi Genzyme collaboration, as amended in January 2018 and April 2019, as well as the Exclusive TTR License and the A&R AT3 License Terms, including the ongoing or expected financial and accounting impact on our business, please read Note 4, Collaboration 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. In December 2019, MDCO filed for regulatory approval of inclisiran in the U.S., and in January 2020, MDCO was acquired by Novartis AG. For more information regarding the MDCO agreement, including its ongoing financial and accounting impact on our business, please read Note 4, Collaboration 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.

Vir Biotechnology, Inc. In October 2017, we and Vir entered into a collaboration and license agreement pursuant to which we granted to Vir an exclusive license to develop, manufacture and commercialize ALN-HBV02 (VIR-2218), for all uses and purposes other than certain excluded fields, as set forth in the agreement. In addition, we granted Vir an exclusive option for up to four additional RNAi therapeutics programs for the treatment of infectious diseases. For more information regarding the Vir agreement, including its ongoing financial and accounting impact on our business, please read Note 4, Collaboration 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, or the 2015 Ionis agreement. 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 extended 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, Collaboration 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, Proprietary Rights and Exclusivities

We have devoted considerable effort and resources through both in-licensing and filing patent applications on our own inventions, as well as protecting our trade secrets and know-how 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;
- compositions of siRNAs directed to specific targets as well as their methods of use, including as therapeutics and diagnostics;
- delivery technologies, such as in the fields of siRNA conjugates, including carbohydrate, lipophilic and other conjugates as well as cationic liposomes and other delivery vehicles; and
- all aspects of our development candidates and marketed products, with an additional level of protection for trademarks related to our marketed products.

In addition to patents and trademarks for our marketed products, we seek to obtain all available regulatory exclusivities for our marketed products, including data and orphan exclusivities in the relevant jurisdictions.

Key Patents and Regulatory Exclusivities

We typically obtain protection of our product candidates with patents and patent applications directed to compositions of matter and their uses. Below is a summary of granted patents that we own or control covering our marketed products in the U.S. and Europe.

ONPATTRO

Patent Number	Country/Region*	Patent Type	Expiration Date**	Owner/Licensor
8168775	United States	Compositions of Matter & Methods of Use	8/10/2032	Alnylam
8334373	United States	Compositions of Matter & Methods of Use	5/27/2025	Alnylam
8741866	United States	Compositions of Matter & Methods of Use	10/20/2029	Alnylam
9234196	United States	Compositions of Matter & Methods of Use	10/20/2029	Alnylam
8802644	United States	Compositions of Matter & Methods of Use	10/21/2030	Arbutus Biopharma
8158601	United States	Compositions of Matter & Methods of Use	11/10/2030	Arbutus Biopharma
9943538	United States	Compositions of Matter	11/4/2023	Ionis Pharmaceuticals
9943539	United States	Compositions of Matter	11/4/2023	Ionis Pharmaceuticals
2937418	Europe	Compositions of Matter & Methods of Use	8/28/2033	Alnylam
2344639	Europe	Compositions of Matter & Methods of Use	10/20/2029	Alnylam
2440183	Europe	Compositions of Matter	10/21/2030	Arbutus Biopharma

* Shown here are selected granted patents in the U.S. and Europe. Additional granted and pending patents in the U.S., Europe and other countries may be available.
** Expiration dates listed here include any granted or anticipated patent term extensions and supplemental protection certificates but exclude any pediatric extensions that may be available.

In addition, in connection with our FDA approval on August 10, 2018, the FDA granted ONPATTRO (patisiran) new chemical entity, or NCE, exclusivity until August 10, 2023, and Orphan Drug Exclusivity, or ODE, until August 10, 2025. In connection with our EMA approval on August 26, 2018, the EMA granted ONPATTRO (patisiran) Marketing Exclusivity and ODE until August 26, 2028.

GIVLAARI

Patent Number	Country/Region*	Patent Type	Expiration Date**	Owner/Licensor
8106022	United States	Compositions of Matter & Methods of Use	12/12/2029	Alnylam
8828956	United States	Compositions of Matter & Methods of Use	12/4/2028	Alnylam
9133461	United States	Compositions of Matter & Methods of Use	5/14/2033	Alnylam/Icahn School of Medicine at Mount Sinai
9150605	United States	Compositions of Matter	8/28/2025	Ionis Pharmaceuticals
9631193	United States	Methods of Use	3/15/2033	Alnylam/Icahn School of Medicine at Mount Sinai
9708610	United States	Compositions of Matter & Methods of Use	1/1/2024	Ionis Pharmaceuticals
9708615	United States	Compositions of Matter & Methods of Use	3/8/2024	Alnylam
10119143	United States	Compositions of Matter & Methods of Use	10/3/2034	Alnylam/Icahn School of Medicine at Mount Sinai
10125364	United States	Compositions of Matter & Methods of Use	3/15/2033	Alnylam/Icahn School of Medicine at Mount Sinai
10131907	United States	Compositions of Matter & Methods of Use	8/24/2028	Alnylam
10273477	United States	Compositions of Matter	3/8/2024	Alnylam
2836595	Europe	Compositions of Matter & Methods of Use	4/10/2033	Alnylam/Icahn School of Medicine at Mount Sinai
2336317	Europe	Compositions of Matter	6/14/2024	Alnylam
2957568	Europe	Compositions of Matter	11/4/2023	Ionis Pharmaceuticals
1560840	Europe	Compositions of Matter	11/4/2023	Ionis Pharmaceuticals

* Shown here are selected granted patents in the U.S. and Europe. Additional granted and pending patents in the U.S., Europe and other countries may be available.
** Expiration dates listed here do not account for any patent term extensions, supplemental protection certificates or pediatric extensions that may be available.

In addition, in connection with our FDA approval on November 20, 2019, the FDA granted GIVLAARI (givosiran) NCE exclusivity until November 20, 2024, and ODE until November 20, 2026.

Trademarks

We file trademarks to protect our corporate brand and our products. Typically we file trademark applications in the U.S., Europe and elsewhere in the world as appropriate. In addition to multiple pending trademark applications in the U.S. and other major countries, we have registered trademarks in the U.S., including but not limited to Alnylam®, Alnylam Pharmaceuticals® and the Alnylam logo, as well as ONPATTRO®, the ONPATTRO logo and GIVLAARI®.

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, or AIA, 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, a third party has filed an opposition in the European Patent Office, or EPO, against our owned patent EP 2723758, with claims directed to compositions and methods of ANGPTL3, arguing that the granted claims are invalid. 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 Pharmaceutical Company Ltd., or 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 Biopharma Corp., or 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., Ascletis 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. Several 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., MiNA 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 collaborators, including Biogen Inc., AstraZeneca PLC and Bayer AG, a number of other companies have ASO-based product candidates in various stages of pre-clinical and clinical development, including Roche, 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 Products and Late-Stage Investigational RNAi Therapeutics

ATTR Amyloidosis. Until recently, liver transplantation was the only treatment option for patients with hATTR amyloidosis in the U.S. and in other countries. 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 wild-type TTR protein.

In addition to ONPATTRO, approved treatments for hATTR amyloidosis now include inotersen (TEGSEDI, approved in the U.S., EU, Canada and Brazil) and tafamidis (VYNDAQEL/VYNDAMAX, approved in many countries). Indications vary by country/region for each product.

Several investigational drugs also 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
VYNDAQEL (tafamidis meglumine)	Pfizer Inc.	Small molecule drug to stabilize TTR protein	Approved in the EU, Japan and certain countries in Latin America for hATTR polyneuropathy (indication varies by region)	Daily oral capsule
VYNDAQEL/VYNDAMAX (tafamidis meglumine / tafamidis)	Pfizer Inc.	Small molecule drug to stabilize TTR protein	Approved to treat ATTR cardiomyopathy in the U.S. and Japan; MAA filed in the EU (indication varies by region)	Daily oral capsule
TEGSEDI (inotersen)	Ionis/Akcea	ASO to reduce production of TTR Protein	Approved in U.S., EU, Canada and Brazil for hATTR polyneuropathy (indication varies by region)	Weekly subcutaneous injection (SC)
AKCEA-TTR-LRx or ION-TTR-LRx	Ionis/Akcea	ASO to reduce production of TTR Protein	Phase 3	Monthly SC
AG10	Eidos Therapeutics, Inc.	Small molecule drug to stabilize TTR protein	Phase 3	Twice daily oral dose
PRX004	Prothena Corporation plc	mAb to clear amyloid deposits	Phase 1	Intravenous (IV)
Diflunisal	N/A (generic)	Non-steroid anti-inflammatory agent	Approved, but not indicated for the treatment of ATTR amyloidosis	Twice-daily oral dose
Tolcapone	SOM Innovation Biotech, S.L.	Small molecule repurposed generic drug	Phase 1/2	Daily oral dose
NTLA-2001	Intellia Therapeutics, Inc.	CRISPR/Cas9 gene therapy	IND application expected in mid-2020	Unknown

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

Acute Hepatic Porphyria. In addition to GIVLAARI, which was recently approved in the U.S. for the treatment of adults with AHP, there are also two approved hemin products, Panhematin (U.S.) and Normosang (EU), for the treatment of acute porphyria attacks. Panhematin and Normosang are both administered by intravenous infusion and are blood products currently manufactured by Recordati S.p.A. There are currently no competing 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 primary hyperoxaluria, or 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 2 (pivotal)	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 AB	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.

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	Approved	SC
Praluent	Sanofi	Anti-PSCK9 mAb	Approved	SC
Vascepa	Amarin Corporation	Omega-3 lipid proven to reduce LDL-C and CV Risk	Approved	Oral
Bempedoic Acid (ETC-1002)	Esperion Therapeutics, Inc.	Oral fatty acid and cholesterol synthesis dual inhibitor	Phase 3	Oral
REGN1500 (evinacumab)	Regeneron	Anti-ANGPTL3 mAb for hypercholesterolemia	Phase 3 in HoFH	SC
Arrowhead- ARO-ANG3	Arrowhead	siRNA targeting ANGPTL3	Phase 1	SC
Akcea-ANGPTL3-Lrx	Akcea / Pfizer	ASO therapy to reduce levels of ANGPTL3	Phase 2	SC

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, if fitusiran receives regulatory approval, along with additional approved drugs and drug candidates not listed below:

Drug (Company)	Drug Description	Phase	Administration
Hemophilia A			
Advate (Takeda), Adynovate (Takeda), 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 - Monthly
Hemophilia B			
Rixubis (Takeda), 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 (Roche, through its acquisition of Spark Therapeutics)	Spark200 AAV FIX gene therapy	Phase 3	IV - Single Administration
Inhibitor Patients			
Emicizumab HEMLIBRA, ACE-910 (Roche)	Bispecific antibody mimetic of FVIII	Approved	SC - Monthly
Feiba (Takeda)	Bypassing agent	Approved	IV
NovoSeven (Novo Nordisk)	Bypassing agent	Approved	IV
Hemophilia A and B			
Concizumab, anti-TFPI (Novo Nordisk)	anti-TFPI antibody	Phase 2	IV
PF – 06741086	Anti-TFPI antibody	Phase 3	IV

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 IND, which must become effective prior to commencement of clinical testing in the U.S., 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 and other conditions of use 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, limit 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, lumasiran 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 Institutional Review Board, or IRB, or the FDA may, at any time, suspend, terminate, significantly modify 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 serious adverse event, or 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 primarily to 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 or patient participating in the study. 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 or require 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 ClinicalTrials.gov, 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, PH1, 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, and thus will require an NDA. FDA approval of an NDA is required before commercial distribution of a 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 an application fee. For fiscal year 2020, the application fee for each NDA requiring clinical data was approximately $2.9 million. PDUFA also imposes an annual program fee for each approved prescription drug, which was set at approximately $325,000 for fiscal year 2020. 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. During that time, the FDA may request additional information rather than accept an NDA for filing. If the FDA determines that an NDA is not sufficiently complete to permit substantive review, it will issue a refuse to file determination and the NDA will not be reviewed by the FDA. 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. For novel drug products or drug products that present difficult questions of safety or efficacy, the FDA will refer to an advisory committee, which is typically in the form of 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 may waive the review of an advisory committee review and 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 or facilities, 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. The approved indication may be narrower than what was proposed by the applicant or narrower than the population studied in clinical trials. As a condition of NDA approval, the FDA may require post-approval evaluations, 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, adverse event, or AE, reporting, submission of other periodic reports, recordkeeping, product sampling and distribution. Additionally, the FDA 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, and requires that important safety information be presented to balance information provided on a drug's effectiveness. 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 the manufacturing facilities for the product are 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 may recommend actions that the applicant can take to address the deficiencies. 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, however, 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 or cleared 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. If the FDA does require separate, additional approvals or clearances for the modified device, the FDA could require either a premarket application, or PMA, a 510(k) clearance, or a *de novo* classification, depending on the risk classification of the modified device and the availability of legally marketed predicate devices. Approval of PMAs are required for class III medical devices, which are devices for which insufficient information exists to provide reasonable assurance of the safety and effectiveness of the device through general controls and special controls. PMAs must contain sufficient valid scientific evidence to assure that the device is safe and effective for its intended use. Clearance under section 510(k) of the FDCA is required for most class II medical devices, which are devices for which special controls are necessary to provide reasonable assurance of safety and effectiveness. A 510(k) submission demonstrates to the FDA that the device is substantially equivalent (i.e., at least as safe and effective) as a legally marketed predicate device that is not subject to PMA requirements. If no such legally marketed predicate device exists, but the applicant believes the device should not be automatically classified into class III, the applicant can submit an application for *de novo* classification, which is a request to FDA to classify the device into class I or II based on certain general and, if applicable, special controls that are necessary to provide reasonable assurance of safety and effectiveness of the device. In addition, if the FDA requires a separate, additional approval or clearance for a delivery device to be used with our products, and 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, described above. 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 a 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 often 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 drug product without such changes.

Federal law also provides a five-year period of NCE exclusivity following approval of a drug that contains an 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 for the listed drug that is listed in the FDA's publication Approved Drug Products with Therapeutic Equivalence Evaluations, commonly referred to as the Orange Book. If the applicant is not seeking approval of a use claimed by a method-of-use patent, however, the applicant can submit a statement to that effect instead of making the certification. These certifications (and statements) affect 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 product before a listed patent expires (i.e., a paragraph III certification), then the FDA will not 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), and certain other steps are taken, then approval of the ANDA or 505(b)(2) application will be stayed (i.e., FDA will not approve the application) until 30 months have passed or patent disputes are resolved, as described below. Specifically, under the process set forth by the statute, the ANDA or 505(b)(2) applicant must 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 court decision or settlement order holds or states that the patents in question are valid, enforceable, and would be infringed, however, then the ANDA or 505(b)(2) application may not be approved until such patents expire. If the patent holder does not initiate a suit for patent infringement within the 45-day time limit described above, 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 Orphan Drug Designation 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. Orphan Drug Designation must be requested before submitting an NDA. After the FDA grants Orphan Drug Designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. We intend to request Orphan Drug Designation for our product candidates, if applicable. For example, the FDA granted Orphan Drug Designation 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 Orphan Drug Designation 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 for a use that is broader than the indication for which it received orphan designation. In addition, orphan drug exclusivity may be lost if the FDA later determines that the Orphan Drug Designation request 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 of 2012, 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 Orphan Drug Designation 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 facilitate development and expedite 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 pre–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 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 drug or biological 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 drug or biological 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 from the date of filing, instead of ten months from the date of filing, except that two months are added to these time periods for drugs that contain a new molecular entity. Additionally, a drug or biological product may be eligible for accelerated approval if it is intended to treat a serious or life-threatening disease or condition, and the product would provide meaningful therapeutic benefit over existing treatments. Under accelerated approval, a product 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 and 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 advance submission of promotional materials prior to use, which could limit or 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 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 of the marketing application. The FDA granted breakthrough therapy designation for patisiran, approved in August 2018, givosiran, approved in November 2019, as well as 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. The American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several types of providers and increased the statute of

limitations period for the government to recover overpayments to providers from three to five years. 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 significantly changed 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% 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.
- 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 offer its innovator products on the Federal Supply Schedule for purchase at prices compliant with statutory and regulatory requirements and 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% 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%.
- 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 (currently defined to include doctors, dentists, optometrists, podiatrists and chiropractors) 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 non-physician providers such as 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 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% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. Various portions of the ACA are currently undergoing legal and constitutional challenges in the Fifth Circuit Court and the United States Supreme Court; the Trump Administration has issued various Executive Orders which have eliminated cost sharing subsidies and various other provisions that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices; and Congress has introduced several pieces of legislation aimed at significantly revising or repealing the ACA. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended. We cannot predict what affect further changes to the ACA would have on our business.

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. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the FCA. 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,as amended, or FCPA, 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.

As described above, the federal Sunshine Act requires manufacturers to report certain payments to health care providers to CMS. 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 2021, 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 2021.

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 European Commission, or 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 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, (ii) the medicine is a significant therapeutic, scientific, or technical innovation, or (iii) if its authorisation 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 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-authorisation obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct

of additional clinical trials or post-authorisation 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 authorisation from the competent national authority. The manufacturer or importer must have a qualified person 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 2019, we filed for regulatory approval of ONPATTRO in Brazil and regulatory filings in additional countries are planned for ONPATTRO and GIVLAARI in 2020, and we will have to follow the specific regulations in Brazil 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.

In Canada, for example, authorization for clinical trials of pharmaceuticals is obtained by way of CTAs. Health Canada (the regulator in Canada that regulates, among other things, research, testing, manufacture and marketing of pharmaceuticals) approval is required for clinical trials using pharmaceuticals not authorized for sale in Canada (e.g., Phases I to III clinical trials and comparative bioavailability studies), and for trials of marketed pharmaceuticals where the proposed use is outside the marketing authorization. In addition, Research Ethics Boards, or REBs, oversee the conduct of clinical trials in Canada, and REB approval is required for each clinical trial site prior to commencing the trial at that site. Post-approval, both Health Canada and the REBs monitor the safety data of the clinical trials and assess serious adverse reactions filed throughout the trial. Health Canada may conduct site inspections to verify whether the conduct of a trial meets the requirements of GCP. An REB may impose conditions in relation to the conduct of clinical trials, and may require the informed consent used in the trial to be amended to address ethical concerns and privacy considerations.

Likewise, in Brazil, if a human clinical trial is to be carried out within the country's territory, in addition to the CTA-like authorization and the approval by an ethics committee, the commencement of the trials may also depend on the approval by a biosecurity commission.

The requirements and process governing the conduct of clinical trials varies from country to country. In all cases, however, 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. Additionally, foreign governments lately are encouraging manufacturers to submit approval application in their jurisdictions with a variety of incentives including favorable reimbursement ratemaking. In Canada, while Health Canada has developed service standards for regulatory review time, those are target or estimated timelines that we can reasonably expect to receive

from the regulator under normal circumstances, and as such, there may be delays in certain situations. In Brazil, obtaining the approval to begin human clinical trials can take from 180 to 360 days, and the marketing approval process itself usually takes between nine to 12 months. On the other hand, many countries have developed programs to expedite the approval of drugs pertaining to certain categories. In Brazil, for example, drugs designed to treat rare diseases can benefit from priority review and obtain marketing approval in less than six months.

With respect to marketing authorization, Canada typically approves pharmaceuticals by way of a Notice of Compliance, or NOC, together with a drug identification number, or DIN. NOCs are issued to pharmaceutical manufacturers following the satisfactory review of a new drug submission. Along with the NOC, a DIN is also issued to indicate the official approval and allow the sponsor to market the pharmaceutical in Canada. A DIN is an eight-digit number and uniquely identifies all pharmaceutical products sold in a dosage form in Canada. Additional obligations must be fulfilled when seeking marketing authorization for biologic medicinal products (whether innovative biologics or biosimilars) in Canada. In addition to the information required for other pharmaceuticals, biologics must include more detailed chemistry and manufacturing information, which ensures the purity and quality of the product. Because slight variations in the manufacturing process can lead to a different product, sponsors must include details of the method of manufacturing in its submission.

Product licensing, pricing and reimbursement vary as well. Canada's pricing of patented pharmaceuticals is controlled by the Patented Medicine Prices Review Board, or PMPRB, whose regulatory authority is established by the Patented Medicines Regulations under Canada's Patent Act. The PMPRB is a regulatory board unique to Canada. Various other regulatory bodies are involved in the pricing of pharmaceuticals that are publicly funded, including the Canadian Agency for Drugs and Technologies in Health, the Institut national d'excellence en santé et en services sociaux, the pan Canadian Pharmaceutical Pricing Alliance, and public payors (e.g., provincial governments and territories). Each province of Canada has its own legislation relating to the pricing and reimbursement of pharmaceuticals, the permitted upcharges for wholesalers and pharmacies, the applicable dispensing fees, and whether rebates and professional allowances to pharmacies are prohibited or permitted. Approximately 40% of pharmaceuticals sold in Canada are paid for by the provincial (public) drug plans; the remainder are sold in the private market (e.g., covered by private insurance or paid for by individuals). The pricing of pharmaceuticals in the private market is less regulated than the pricing of pharmaceuticals in the public market.

In Brazil, price ceiling is government-regulated and must be approved by a specific commission prior to marketing. Since Brazil has a public health system that aims to provide free treatment and care to its whole population, public procurement follows a specific process that requires drugs to be included in the system's formularies prior to being distributed to patients cost-free.

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. In Canada, contravention of the federal Food and Drugs Act, or F&DA, (governs all aspects of the manufacturing, importing, labelling, distribution and sale of pharmaceuticals) and its regulations may result in various enforcement actions from Health Canada, including notice letters, request for plan for corrective measures, public advisories, additional restrictions to our licenses or product authorization, recall, seizure, forfeiture and destruction of our products, refusal, suspension, cancellation or revocation of our authorization, license or registration. In the event of a contravention of the F&DA, Health Canada determines the most appropriate level of intervention depending on the severity of the risk posed by regulatory non-compliance. In certain circumstances, the regulatory enforcement responses are not appropriate to achieve compliance, and Health Canada may investigate potential criminal offences under the F&DA and/or refer to law enforcement for prosecution in relation to offences under the F&DA and the Criminal Code of Canada. The F&DA contains criminal provisions which allow for the issuance of fines, a term of imprisonment, or both.

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 and commercial supply. We expect to continue to rely on third-party CMOs for the supply of drug substance and drug product, including ONPATTRO and GIVLAARI, as well as other product candidates, for at least the next several years, including to support the potential launch of our product candidates 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. 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 and GIVLAARI for both clinical and commercial use. We entered into a manufacturing services agreement with Agilent for ONPATTRO commercial supply and are finalizing an agreement for commercial supply of GIVLAARI. Pursuant to the Agilent supply agreement for ONPATTRO, we are required to provide rolling forecasts 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. We are also constructing a cGMP manufacturing facility in Norton, MA for drug substance for clinical and eventually, 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 patisiran for use in our Phase 2 OLE and Phase 3 clinical trials. We will continue to manufacture commercial supply for formulated bulk drug product for ONPATTRO 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 completing, 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 - starting in 2018, we 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 continued to build a global commercial operation which has been designed to be fully integrated and to sequentially manage multiple product launches across multiple geographies. As a recent commercial-stage biopharmaceutical company, we have been 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 and with collaborators 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 two approved products and our late-stage clinical programs:

- With respect to our ATTR amyloidosis franchise, we have global rights to develop and commercialize both the approved product, ONPATTRO, and the investigational RNAi therapeutic vutrisiran, the next potential product in late-stage development in this franchise;
- For GIVLAARI, approved in the U.S., and lumasiran, we have global rights to develop and commercialize;
- For inclisiran, we have granted MDCO, which was acquired by Novartis AG in January 2020, global rights to develop and commercialize; and
- 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.

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. ONPATTRO and GIVLAARI, as well as the late-stage programs we are advancing internally 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, GIVLAARI 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 in these under-diagnosed diseases.

In addition, with respect to GIVLAARI, in August 2019, we announced that we entered into a U.S. GI disease education and promotional agreement with Ironwood to leverage Ironwood's capabilities in GI to help raise AHP awareness and bring GIVLAARI to gastroenterologists and other HCPs. In the U.S. Ironwood's clinical sales specialists are now promoting GIVLAARI to the gastroenterologists and other HCPs that it already calls on for its marketed product, and we believe this partnership represents a significant opportunity to expand medical education and diagnosis for patients with AHP.

Separately, we have a proactive market access strategy that includes using value-based agreements, or VBAs, that we have formed with commercial payers in the U.S. With respect to ONPATTRO, as of the beginning of 2020, we have completed VBAs with multiple commercial payers, including each of the top five commercial payers and eight of the top ten, with signed VBAs now covering over 130 million U.S. lives in the aggregate. In addition, we have made significant progress toward establishing VBAs for GIVLAARI, including a new ultra-rare disease Prevalence Based Adjustment framework, with multiple discussions ongoing with payers. We believe we have also been making strong progress in the EU with government payers with respect to ONPATTRO. Once a patient is diagnosed and is prescribed ONPATTRO or GIVLAARI in the U.S., 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 our commercially approved products around the world and preparing for the anticipated commercial launches of additional RNAi therapeutics we are developing, including lumasiran, assuming regulatory approval. With respect to commercially approved products, throughout 2019, we continued to build our commercial capabilities, and now have approximately 250 employees in customer facing activities in the U.S. and across the world. We also assembled field teams in the U.S. and other global markets, and are continuing to expand these capabilities to additional countries globally. We are continuing to build 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 also continuing to incorporate 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 built for ONPATTRO to also support the launch of GIVLAARI, as well as the potential launches of lumasiran, assuming regulatory approval, and vutrisiran, assuming positive Phase 3 results and regulatory approval. 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. Our objective is to continue to execute successful product launches leveraging our positive experience with the launch of ONPATTRO.

Employees

At December 31, 2019, we had 1,323 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 675 West Kendall Street, Henri A. Termeer Square, 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 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," "target," "goal" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Any or all of our forward-looking statements in this annual report on Form 10-K and in any other public statements we make may turn out to be wrong. They can be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Many factors mentioned in the discussion below will be important in determining future results. Consequently, no forward-looking statement can be guaranteed. Actual future results may vary materially from those anticipated in forward-looking statements. We explicitly disclaim any obligation to update any forward-looking statements to reflect events or circumstances that arise after the date hereof. You are advised, however, to consult any further disclosure we make in our reports filed with the SEC.

Risks Related to Our Business

Risks Related to Our Financial Results and Need for Financing

We have limited experience as a commercial company and the marketing and sale of ONPATTRO, GIVLAARI 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, and we have since received approval in several additional territories. To date, we have launched ONPATTRO in the U.S., Japan, Canada and in several countries in Europe. In addition, in November 2019, the FDA approved our second product, GIVLAARI (givosiran) injection for subcutaneous use for the treatment of adults with AHP. While we have commercially launched ONPATTRO and GIVLAARI, 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, including lumasiran, which is under review by the FDA for marketing approval. To execute our business plan of building a multi-product, commercial-stage biopharmaceutical company and achieving a self-sustainable financial profile in the future, in addition to successfully marketing and selling ONPATTRO and GIVLAARI, 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 and GIVLAARI, 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, successfully commercialize ONPATTRO, GIVLAARI or any future products, raise capital, expand our business, achieve financial self-sustainability or continue our operations.

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

We have experienced significant operating losses since our inception. As of December 31, 2019, we had an accumulated deficit of $3.73 billion. Although to date we have launched ONPATTRO in the U.S. and several other countries globally, launched GIVLAARI in the U.S., and expect to launch our commercially approved products in additional countries during 2020, we may never attain profitability or positive cash flow from operations. For the year ended December 31, 2019, we recognized $166.5 million in net product revenues from sales of ONPATTRO and GIVLAARI. While we believe 2019 was our peak net loss year, we expect to continue to incur annual net operating losses for the foreseeable future 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 our current and future, if any, commercially approved products, 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 become and/or continue 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 as a commercial company, and may never generate revenues that are significant enough to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. If we cannot become and remain consistently profitable, the market price of our common stock could decline. In addition, we may be unable to raise capital, expand our business, develop additional product candidates or continue our operations.

We will require substantial additional funds to continue 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, GIVLAARI and any other products that are approved for commercial sale. Because the length of time or activities associated with successful development of our product candidates may be greater than we anticipate, we are unable to estimate the actual funds we will require to develop and commercialize them.

We believe 2019 was our peak net loss year, and believe we are on a path toward attaining self-sustainability in our business, however, 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 GIVLAARI 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 may do so through either collaborative arrangements, public or private equity offerings or debt financings, or a combination of one or more of these funding sources. Additional funds may not be available to us on acceptable terms or at all.

In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. 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, any debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets. If an event of default were to occur under any such financing, the interest rate could increase and the lenders could be entitled to take various actions, including the acceleration of amounts due under the loan. Our ability to satisfy and meet any future 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.

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 long-term strategic goals 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.

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 and resulting revenues, 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 substantially decline.

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.

As of December 31, 2019, we had $1.54 billion in cash, cash equivalents and marketable debt and equity securities, excluding the $14.8 million of restricted investments related to the security deposit for the lease of our corporate headquarters in 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.

Changes in tax law could adversely affect our business and financial condition.

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. In the U.S., the rules dealing with federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations.

Additionally, the Organization for Economic Co-operation and Development, or OECD, the EC, and individual taxing jurisdictions where we and our affiliates do business have recently focused on issues related to the taxation of multinational corporations. The OECD has released its comprehensive plan to create an agreed set of international rules for fighting base erosion and profit shifting. In addition, the OECD, the EC and individual counties are examining changes to how taxing rights should be allocated among countries considering the digital economy. As a result, the tax laws in the U.S. and other countries in which we and our affiliates do business could change on a prospective or retroactive basis and any such changes could materially adversely affect our business.

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 commercial capabilities, including in marketing, sales, market access and distribution, to support our wholly-owned products. We also continue to advance our growing pipeline of RNAi therapeutic opportunities. However, we may not have adequate capacity or capabilities to advance all of our 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, as a result of our broad strategic alliance with Sanofi Genzyme formed in 2014, Sanofi Genzyme is now developing and commercializing fitusiran globally. In addition, we formed a collaboration with MDCO (which was acquired by Novartis AG in January 2020) 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. With respect to our CNS/Ocular Disease pipeline, in April 2019, we announced a global, strategic collaboration with Regeneron to discover, develop and commercialize RNAi therapeutics for a broad range of diseases by addressing therapeutic targets expressed in the eye and CNS, in addition to a select number of targets expressed in the liver.

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) Regeneron for the development and commercialization of all programs targeting eye diseases (subject to limited exceptions), and potentially other CNS and liver programs, (ii) MDCO for all future development and commercialization of inclisiran worldwide, and (iii) Sanofi Genzyme for the development and commercialization of fitusiran worldwide. In the case of each such collaboration referenced in clauses (i)-(iii) above, we are entitled to royalties on the sales of each of these products. If our collaborators are not successful in their development and/or commercialization efforts, our future revenues from RNAi therapeutics for these indications may be adversely affected.

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 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 give rise to concerns around the safety and/or efficacy of our technology platform or product candidates. In addition, the occurrence of a fatal thrombotic SAE in our fitusiran study in 2017 could contribute to further concerns about the safety of our therapeutic candidates. Even when we succeed in securing 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 Regeneron, MDCO, Vir and Sanofi Genzyme. 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 these product candidates 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, our agreement with MDCO, which was acquired by Novartis AG in January 2020, relating to the development and commercialization of inclisiran worldwide may be terminated by MDCO at any time upon four months' prior written notice, provided if the agreement is terminated by MDCO for convenience, MDCO has agreed to grant a license to us under certain of our technology developed in the course of MDCO's activities under the agreement, subject to a royalty to be negotiated between the parties. 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.

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, as in the case of MDCO and Novartis AG, 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 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 ONPATTRO and GIVLAARI, 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 completing construction of a cGMP manufacturing facility for drug substance for clinical and, eventually, 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 ONPATTRO, GIVLAARI 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 GIVLAARI, and we have entered into a manufacturing services agreement with Agilent for such supply of ONPATTRO and are finalizing an agreement for the commercial supply of GIVLAARI. 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, supply delays and shortages. 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, GIVLAARI 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 and/or our marketed products, 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:

- 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.

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 commercial experience and newly established capabilities for marketing, sales, market access and distribution, and expect to continue to invest significant financial and management resources to continue to build these capabilities and to establish a global commercial infrastructure. Even if we build and scale our commercial capabilities, the market may not be receptive to our commercial products.

We have limited commercial experience and newly established capabilities for marketing, sales, market access and distribution. We currently expect to rely heavily on third parties to launch and market certain of our product candidates in certain geographies, if approved. However, we intend to commercialize ONPATTRO and GIVLAARI, as well as several of our late-stage product candidates if approved, including lumasiran and vutrisiran, on our own globally. Accordingly, we have developed internal marketing, sales, market access and distribution capabilities as part of our core product strategy initially in the U.S. and the EU, with expansion ongoing globally, which has, and will continue to, require significant financial and management resources. For those products for which we will perform marketing, sales, market access and distribution functions ourselves, including ONPATTRO, GIVLAARI and, if approved, 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:

- developing and retaining our global sales, marketing and administrative infrastructure and capabilities;
- hiring, training, managing and supervising our personnel worldwide;
- the cost of establishing, or leveraging an established, marketing or sales force, which 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 marketing, sales, market access and distribution capabilities for ONPATTRO, GIVLAARI and any future products, we will not be able to successfully commercialize our products without reliance on third parties.

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. These investigators and CROs are not our employees and we have limited control over the amount of time and resources they dedicate to our programs. These third parties may have contractual relationships with other entities, some of which may be our competitors, which may draw their time and resources away from our programs. 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 Pharmaceuticals and Medical Devices Agency 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.

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 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, sales 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 long-term strategic goals. 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 a lesser 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 approved products and as a result, we may be unable to attract and retain highly qualified sales and marketing professionals to support ONPATTRO, GIVLAARI 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 continue to 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 launches of approved products, 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 Asia and Latin America. To date, we have received regulatory approval for ONPATTRO in the U.S. and EU and other countries globally, and as a result of the January 2018 amendment to our Sanofi Genzyme collaboration, we now have global development and commercialization rights for ONPATTRO. In addition, in November 2019, we received FDA approval for our second RNAi therapeutic, GIVLAARI. We have filed an MAA for givosiran with the EMA and expect approval in 2020, and have also filed for marketing approval in Brazil. We plan to file for additional regulatory approvals for both ONPATTRO and GIVLAARI in additional countries during 2020 and beyond.

As noted above, we grew our workforce significantly from 2016 through 2019, and anticipate continuing to hire additional employees globally during 2020 as we focus on the commercialization of ONPATTRO and GIVLAARI and achieving our long-term strategic goals. This growth has placed a strain on our administrative and operational infrastructure and, as a result, 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 global operations in the U.S., the EU, Japan, Latin America 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 we continue the commercialization of ONPATTRO and GIVLAARI, and as the 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 enhance our operational, financial and management controls and systems, reporting systems and infrastructure, and policies and procedures. We may not be able to implement enhancements 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 GIVLAARI, 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 and regulatory guidance relating to such use are evolving and not always clear. This evolution creates uncertainty and risk of noncompliance with regulations applicable to our business, resulting in potential regulatory actions against us, along with the potential for litigation related to off-label marketing or other prohibited activities. For example, for our clinical-stage candidates, 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 study enrollment may be adversely impacted, we fail to monitor and comply with applicable AE reporting obligations or that 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 online platform, including a blog on the internet, or a post on a website, that can be distributed rapidly and could negatively harm our reputation. 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. The UK officially withdrew from the EU on January 31, 2020, however the effects of the

departure on both the EU and the UK are still highly uncertain, as many details of the divorce have yet to be addressed. The 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. 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 or our partners 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 internal and partnered programs in Phase 3 development, as well as several earlier-stage clinical programs. In December 2019, we reported positive topline results from our ILLUMINATE-A Phase 3 clinical trial for lumasiran, an investigational RNAi therapeutic targeting GO in development for the treatment of PH1, and initiated a rolling submission of an NDA in January 2020. We expect to submit an MAA and complete our NDA submission in early 2020. However, we may not be able to further advance this or any other product candidate through clinical trials and regulatory approval.

Additionally, several of our planned and ongoing clinical trials utilize an “open-label” trial design. An “open-label” clinical trial is one where both the patient and investigator know whether the patient is receiving the investigational product candidate or either an existing approved drug or placebo. Most typically, open-label clinical trials test only the investigational product candidate and sometimes may do so at different dose levels. Open-label clinical trials are subject to various limitations that may exaggerate any therapeutic effect as patients in open-label clinical trials are aware when they are receiving treatment. Open-label clinical trials may be subject to a “patient bias” where patients perceive their symptoms to have improved merely due to their awareness of receiving an experimental treatment. In addition, open-label clinical trials may be subject to an “investigator bias” where those assessing and reviewing the physiological outcomes of the clinical trials are aware of which patients have received treatment and may interpret the information of the treated group more favorably given this knowledge. The results from an open-label trial may not be predictive of future clinical trial results with any of our product candidates for which we include an open-label clinical trial when studied in a controlled environment with a placebo or active control.

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. 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, ONPATTRO, GIVLAARI and our current product candidates, including lumasiran, vutrisiran, fitusiran and inclisiran, each employ novel delivery technologies that, with the exception of inclisiran, 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 Data Monitoring Committee, or 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 ONPATTRO 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 or 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 had discontinued a Phase 2 study of cemdisiran in atypical hemolytic uremic syndrome and are focusing 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; injection site reactions, or ISRs, were reported in 12 patients. In August 2015, we reported that three patients had discontinued from the revusiran Phase 2 OLE study due to recurrent localized reactions at the injection site or a diffuse rash; no further discontinuations due to ISRs had occurred as of May 26, 2016.

In our ENVISION Phase 3 study of givosiran in patients with AHP, AEs were reported in 89.6% of givosiran patients and 80.4% of placebo patients; SAEs were reported in 20.8% of givosiran patients and 8.7% of placebo patients. Of the SAEs reported in givosiran patients, there were two cases of CKD, and one case each of asthma, device-related infection, gastroenteritis, hypoglycemia, abnormal liver function test, major depression, pain management and pyrexia. Three SAEs in givosiran patients were reported as related to study drug: pyrexia, abnormal liver function test and CKD. The two SAEs of CKD noted above were considered serious due to elective hospitalization for diagnostic evaluation. There were no deaths in the study. One patient in the givosiran arm discontinued treatment due to an increase in alanine aminotransferase, or ALT, level greater than eight times the upper limit of normal, a protocol-defined stopping rule. The increase in ALT levels subsequently resolved. AEs reported in greater than 10% of givosiran patients and seen more frequently compared to placebo were nausea, ISRs, CKD, and fatigue. Four of five of the patients with AEs reported as CKD had a prior history of CKD or a baseline estimated glomerular filtration rate less than 60 mL/min/1.73 m^2. No patients had clinically significant proteinuria and there were no treatment discontinuations due to renal AEs.

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;
- 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 for our product candidates and, as a result, we may be unable to commercialize such 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.

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. In July 2019, we filed a MAA for givosiran. The EMA has validated the MAA and granted an accelerated assessment for givosiran. Any delay in the review or potential approval of givosiran by the EMA could adversely impact our business.

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 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, and in several other geographies during 2019, and GIVLAARI, which was approved in the U.S. in November 2019, 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, GIVLAARI or other drug products required as a condition of approval or agreed to by us. The regulatory approvals that we receive for ONPATTRO and GIVLAARI, 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 plan after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug. As ONPATTRO and GIVLAARI are 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 or GIVLAARI may be more modest than originally anticipated;
- regulatory approvals for ONPATTRO or GIVLAARI may be restricted or withdrawn;
- 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 plan, 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 or GIVLAARI, increase our expenses and impair our ability to successfully commercialize either ONPATTRO or GIVLAARI.

The CMO and manufacturing facilities we use to make ONPATTRO, GIVLAARI 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 and the EMA in connection with the review of our applications for regulatory approval for ONPATTRO and GIVLAARI, and may be subject to similar inspection in connection with any subsequent applications for regulatory approval of ONPATTRO or GIVLAARI filed in other territories or in connection with the pending FDA regulatory application for lumasiran. 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 completing construction of a cGMP manufacturing facility for drug substance for clinical and, eventually, 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 favorably with other available options, including inotersen, marketed by Akcea, which is administered subcutaneously, or tafamidis, marketed by Pfizer, 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.

The patient populations suffering from hATTR amyloidosis and AHP are small and have not been established with precision. If the actual number of patients is smaller than we estimate, or if we cannot raise awareness of these diseases and diagnosis is not improved, our revenue and ability to achieve profitability from ONPATTRO and GIVLAARI may be adversely affected.

Our estimates regarding the potential market size for ONPATTRO, GIVLAARI or any future products, including lumasiran, at the time we commence commercialization, may be materially different from the actual market size, 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. In addition, as is the case with most orphan diseases, if we cannot successfully raise awareness of these diseases and improve diagnosis, it will be more difficult or impossible to achieve profitability.

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

Physicians have the discretion to prescribe approved 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 that approve drug products do not regulate a physician's practice of medicine or 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, including by their agents. Manufacturers and their agents may not promote drugs for off-label uses or provide off-label information in the promotion of drug products that is not consistent with the approved labeling for those products. For example, 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 corrective advertising in addition 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, and we intend to engage in medical education activities and communicate with healthcare providers in compliance with all applicable laws and regulatory guidance. Nonetheless, the FDA, other applicable regulatory authorities, competitors, and other third parties may take the position that we are not in compliance with such regulations, and if such non-compliance is proven, it could harm our reputation, financial condition or divert financial and management resources from our core business, and would have a material adverse effect on our business, financial condition and results of operations. Moreover, any threatened or actual government enforcement actions or lawsuits by third parties could also generate adverse publicity, which could decrease demand for our products and require that we devote substantial resources that could be used productively on other aspects of our business.

In addition to our medical education efforts, we also offer patient support services to assist patients receiving treatment with our commercially approved products. 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 a compliant corporate culture and compliance with such laws.

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 and GIVLAARI 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 and GIVLAARI, 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, GIVLAARI or any future products, including lumasiran, 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, GIVLAARI 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, GIVLAARI 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 have entered into more than ten VBAs and are negotiating additional VBAs for ONPATTRO with certain private health insurers. In addition, we have made significant progress toward establishing VBAs for GIVLAARI. The goal of these agreements is to ensure that we are paid based on the ability of our commercially approved products to deliver results in the real world setting comparable to those demonstrated in clinical trials. Partnering with payers 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 our commercially approved products' performance in real-world use to financial terms. If the price we are able to charge for ONPATTRO, GIVLAARI 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% 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.

Some of the drugs we market need to be administered under the supervision of a physician or other healthcare professional on an outpatient basis, including ONPATTRO and GIVLAARI. 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. For example, on December 18, 2019, President Trump, the U.S. Department of Health and Human Services, and the FDA issued a notice of proposed rulemaking that, if finalized, would allow for the importation of certain prescription drugs from Canada. FDA also issued a Draft Guidance document outlining a potential pathway for manufacturers to obtain an additional National Drug Code for an FDA-approved drug that was originally intended to be marketed in a foreign country and that was authorized for sale in that foreign country. The regulatory and market implications of the notice of proposed rulemaking and Draft Guidance are unknown at this time, but legislation, regulations or policies allowing the reimportation of drugs, if enacted and

implemented, could decrease the price we receive for our products and adversely affect our future revenues and prospects for profitability. 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, GIVLAARI 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, GIVLAARI 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.
- Pharmaceutical companies are required to offer discounts on brand-name drugs to patients who fall within the Medicare Part D coverage gap, commonly referred to as the “donut hole.”
- Pharmaceutical companies are required to pay an annual non-tax deductible fee to the federal government based on each company’s market share of prior year total sales of branded products to certain federal healthcare programs, such as Medicare, Medicaid, Department of Veterans Affairs and Department of Defense. Since we expect our branded pharmaceutical sales to constitute a small portion of the total federal healthcare program pharmaceutical market, we do not expect this annual assessment to have a material impact on our financial condition.
- The law provides that approval of an application for a follow-on biologic product may not become effective until 12 years after the date on which the reference innovator biologic product was first licensed by the FDA, with a possible six-month extension for pediatric products. After this exclusivity ends, it will be easier for generic manufacturers to enter the market, which is likely to reduce the pricing for such products and could affect our profitability.
- The 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% 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 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2029 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, GIVLAARI or any of our product candidates for which we may obtain regulatory approval, or the frequency with which ONPATTRO, GIVLAARI 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.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. Various portions of the ACA are currently undergoing legal and constitutional challenges in the Fifth Circuit Court and the United States Supreme Court; the Trump Administration has issued various Executive Orders which eliminated cost sharing subsidies and various provisions that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices; and Congress has introduced several pieces of legislation aimed at significantly revising or repealing the ACA. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended. We cannot predict what affect further changes to the ACA would have on our business. The costs of prescription pharmaceuticals in the U.S. have 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, increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. 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 was considering issuing a proposed rule in 2019 on a model called the International Pricing Index, with a potential start in the spring of 2020. To date, a proposed rule has not yet been released. 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. Although some of these, and other, proposals related to the administration's Blueprint may require additional authorization to become effective, may ultimately be withdrawn, or may face challenges in the courts, the Congress and the Trump administration have indicated that they will continue to seek new legislative and administrative measures to control drug costs. For example, on September 25, 2019, the Senate Finance Committee introduced the Prescription Drug Pricing Reduction Act of 2019, a bill intended to reduce Medicare and Medicaid prescription drug prices. The proposed legislation would restructure the Part D benefit, modify payment methodologies for certain drugs, and impose an inflation cap on drug price increases. Another bill, the Lower Drug Costs Now Act of 2019, which passed out of the House of Representatives on December 12, 2019, and would require the U.S. Department of Health and Human Services to directly negotiate drug prices with manufacturers. It is unclear whether either of these bills will make it through both chambers of Congress and be signed into law, and if either is enacted, what effect it would have on our business; however enactment of either of these bills could have a material adverse effect on our business and prospects.

At the state level, 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, GIVLAARI 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.

We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, and anti-money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic and international markets. We can face criminal liability and other serious consequences for violations, which can harm our business.

We are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls, the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and other state and national anti-bribery and anti-money laundering laws in the countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. From time to time, we may engage third parties for clinical trials outside of the United States, to sell our products abroad, and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, contractors, and other collaborators, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences.

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, or Japan, 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. Moreover, 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, GIVLAARI or any future products in those countries would be negatively affected. Another impact from the tightening pricing control could be felt from greater competition from less expensive generic or biosimilar products once the exclusivity expires; the governments have adopted policies to switch prescribed products to generic versions in order to cut the medical cost.

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 imposes requirements relating to the privacy, security, and transmission of individually identifiable health information; and requires notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information.
- The U.S. federal Open Payments requirements, which were implemented by the CMS pursuant to the Physician Payments Sunshine Act as part of the ACA. 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 made to physicians (currently defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals as well as ownership and investment interests held by physicians and their immediate family members. Legislation passed in 2018 expands the scope of covered recipients to non-physician provider such as physician assistants and advanced practice nurses, effective in 2022.
- Federal statutory and regulatory requirements applicable to pricing and sales of product to Federal Government Agencies.
- 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 (202/58/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.
- The California Consumer Privacy Act of 2018, or CCPA, effective as of January 1, 2020, that gives California residents expanded rights to access and require deletion of their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation.

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 provides 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 4% 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 commercial launches of ONPATTRO in the third quarter of 2018, and GIVLAARI in December 2019, and as we prepare for the launch in additional countries, 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 GIVLAARI, 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;
- untitled letters or 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.

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 4% 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. 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. Draft regulations were rejected by the Permanent Representatives Committee of the Council of EU on November 22, 2019; it is not clear when new regulations will be adopted in 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 2% 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 2029 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, GIVLAARI 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 and GIVLAARI, 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 and GIVLAARI. 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.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements or insider trading violations, which could significantly harm our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with governmental regulations, comply with healthcare fraud and abuse and anti-kickback laws and regulations in the U.S. and abroad, or failure to report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of, including improper trading based upon, information obtained in the course of clinical studies, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a code of business conduct and ethics and a robust compliance program, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

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 and Norton 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 and Norton facilities comply with the relevant guidelines of the City of Cambridge, the town of Norton, 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 compositions, 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 subject matter 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 or our licensees may be required to obtain licenses under third-party patents to market ONPATTRO or GIVLAARI or further develop and commercialize future products such as lumasiran and inclisiran, currently under review with the FDA, or continuing to develop candidates in our pipeline being developed by us or our licensees. If licenses are not available to us or not available on reasonable terms, we or our licensees 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 United States Patent and Trademark Office, or USPTO, may commence interference proceedings involving our patents or patent applications. Any challenge to, finding of unenforceability or invalidation or circumvention of, our patents or patent applications, would be costly, would require significant time and attention of our management, 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 AIA 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 AIA, 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 Ltd., Ionis, the Massachusetts Institute of Technology, or MIT, Whitehead Institute for Biomedical Research, or Whitehead, Max Planck Innovation GmbH (formerly known as Garching Innovation GmbH), or Max Planck, 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 AIA, which became available to third party challengers on September 16, 2012, in various patent offices relating to patent rights in the RNAi field. In addition, third parties may challenge the validity of our patents. For example, a third party has filed an opposition in the EPO against our owned patent EP 2723758, with claims directed to compositions and methods of ANGPTL3, arguing that the granted claims are invalid. 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. Even if our rights are not directly challenged, disputes could lead to the weakening of our intellectual property rights. Our defense against any attempt by third parties to circumvent or invalidate our intellectual property rights could be costly to us, could require significant time and attention of our management and could have a material adverse effect on our business and our ability to successfully compete in the field of RNAi.

There are many issued and pending patents that claim aspects of oligonucleotide chemistry and modifications that we may need for our siRNA marketed products ONPATTRO and GIVLAARI, our late-stage therapeutic candidates being developed by us or our licensees, including lumasiran, inclisiran and fitusiran as well as our other pipeline products. 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 and GIVLAARI, or further develop and commercialize future products such as lumasiran and inclisiran, currently under review with the FDA, or continuing to develop candidates in our pipeline being developed by us or our licensees. 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 GIVLAARI, 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.

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 Sharp & Dohme Corp., or 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 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 the University of Massachusetts, 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 issue an injunction requiring us to stop the infringing activity or obtain a license. Any license required under any patent may not be made available on commercially reasonable 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, GIVLAARI 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 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, denying any liability to Ionis and the matter is currently in the expert discovery phase. The arbitration has been set for hearing in the first half of 2020. 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, GIVLAARI 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, GIVLAARI 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, which is now approved in the U.S., the EU, Japan and certain countries in Latin America, and inotersen, developed by Ionis and licensed to Akcea, which is now approved in the U.S., the EU, Canada and Brazil, as well as product candidates in various stages of clinical development, including an additional investigational drug being developed by Ionis. Finally, we are aware that Eidos Therapeutics, Inc., or Eidos, initiated a Phase 3 clinical trial of AG10, a TTR stabilizer, in ATTR-CM in February 2019. Eidos also plans to initiate a Phase 3 clinical trial of AG10 in ATTR-PN patients in the first quarter of 2020. While we believe that ONPATTRO has and will continue to 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.

We are aware of product candidates in various stages of clinical development for the treatment of PH1 which would compete with lumasiran, our investigational RNAi therapeutic now in Phase 3 studies for the treatment of this disease, including Oxabact®, a bacteria-based investigational therapy in Phase 3 development by OxThera AB, reloxaliase an investigational enzyme therapy in Phase 2 development for primary or severe secondary hyperoxaluria by Allena Pharmaceuticals, Inc., and DCR-PHXC, an investigational RNAi therapeutic in development by Dicerna for the treatment of PH. In July 2019, the FDA granted a Breakthrough Therapy Designation to DCR-PHXC for the treatment of patients with PH, and in November 2019, Dicerna announced that it initiated dosing in PHYOX2 pivotal clinical trial of DCR-PHXC that is expected to enroll approximately 36 patients with PH1 and PH type 2. 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 and its collaborators, 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 AG, has obtained specific exclusive licenses for 30 gene targets, that include access to certain aspects of our technology. 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, Canada and Brazil, 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. The complaint, as further amended, alleges that we and our Chief Executive Officer, former Chief Financial Officer and certain of our other executive officers 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 September 20, 2017 and September 12, 2018. We believe that the allegations contained in this 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. For example, on September 12, 2019, the Chester County Employees Retirement Fund, individually and on behalf of all others similarly situated, filed a purported securities class action complaint for violation of federal securities laws against us, certain of our current and former directors and officers, and the underwriters of our November 14, 2017 public stock offering, in the Supreme Court of the State of New York, New York County. 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.

Future sales of shares of our common stock, including by our significant stockholders, us or our directors and officers, could cause the price of our common stock to decline.

A small number of our stockholders beneficially own a substantial amount of our common stock. As of December 31, 2019, our six largest stockholders beneficially owned in excess of 50% of our outstanding shares of common stock. If our significant stockholders, or we or our officers and directors, sell substantial amounts of our common stock in the public market, or there is a perception that such sales may occur, the market price of our common stock could be adversely affected. Sales of common stock by our significant stockholders might make it more difficult for us to raise funds by selling equity or equity-related securities in the future at a time and price that we deem appropriate.

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

As of May 21, 2019, the closing date of the stock purchase in connection with the 2019 Regeneron collaboration, Regeneron held approximately 4% of our outstanding common stock and has the right to increase its ownership up to 30%. This concentration of ownership could harm the market price of our common stock in the future by:

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

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

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

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

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

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 or own as of January 31, 2020 is included in the table below.

Location	Primary Use	Approximate Square Footage	Lease Expiration Date	Renewal Option
675 West Kendall Street Cambridge, Massachusetts	Corporate headquarters and primary research facility	295,000	January 2034	Two five-year terms
300 Third Street Cambridge, Massachusetts	Office space and additional research facility	129,000	January 2034	Two five-year terms
101 Main Street Cambridge, Massachusetts	Office space	72,000	June 2021 and March 2024	One five-year term on each lease
20 Commerce Way Norton, Massachusetts	cGMP manufacturing*	200,000	Not applicable	Not applicable
665 Concord Avenue Cambridge, Massachusetts	cGMP manufacturing**	15,000	August 2022	One five-year term
Grafenauweg 4 6300 Zug	International headquarters	14,500	March 2023	One five-year term
Braywick Gate Braywick Road, Maidenhead Berkshire, United Kingdom	Office space	21,500	May 2026	None
Wisdom Cross Tower Antonio Vivaldistraat 150 Amsterdam, Netherlands	Office space***	12,500	April 2025	One five-year term

* We are completing construction of a manufacturing facility at this site for drug substance for clinical and eventually commercial use.

** We manufacture ONPATTRO (patisiran) formulated bulk drug product at this location.

*** We executed a lease for a new office space in Amsterdam in the fourth quarter of 2019. The lease commencement date is March 1, 2020.

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

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 the section titled "Litigation" within Note 9, Commitments and Contingencies, to our consolidated financial statements included in Part II, Item 8, “Financial Statements and Supplementary Data,” of this annual report on Form 10-K, which is incorporated into this item by reference.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

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

Market Information

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

Holders of record

At January 31, 2020, there were 29 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

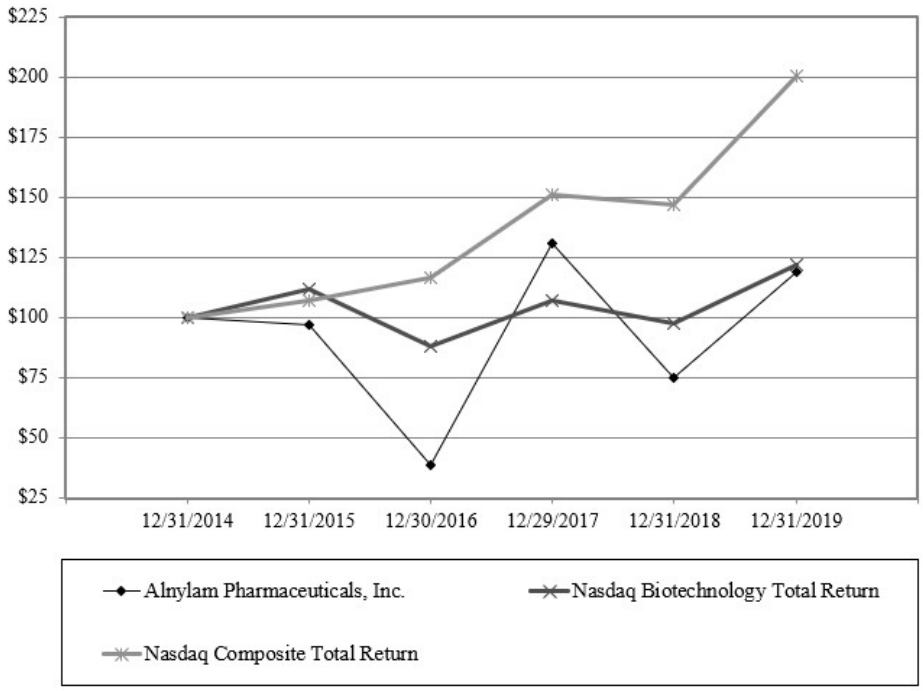
We intend to file with the SEC a definitive Proxy Statement, which we refer to herein as the Proxy Statement, not later than 120 days after the close of the fiscal year ended December 31, 2019. The information required by this item relating to our equity compensation plans is incorporated herein by reference to the information contained under the section captioned "Equity Compensation Plan Information" of the Proxy Statement.

Stock Performance Graph

The following performance graph and 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, 2014, to the close of the last trading day of 2019, 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



	12/31/2014	12/31/2015	12/30/2016	12/29/2017	12/31/2018	12/31/2019
Alnylam Pharmaceuticals, Inc.	$ 100.00	$ 97.05	$ 38.60	$ 130.98	$ 75.16	$ 118.73
Nasdaq Composite Total Return	$ 100.00	$ 106.96	$ 116.45	$ 150.96	$ 146.67	$ 200.49
Nasdaq Biotechnology Total Return	$ 100.00	$ 111.77	$ 87.91	$ 106.92	$ 97.45	$ 121.92

ITEM 6. SELECTED CONSOLIDATED FINANCIAL DATA

The following selected consolidated financial data for each of the five years in the period ended December 31, 2019 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,				
	2019	2018 (2)	2017	2016	2015
Statements of Operations Data:					
Revenues	$ 219,750	$ 74,908	$ 89,912	$ 47,159	$ 41,097
Operating costs and expenses (1)	1,159,181	889,581	590,000	471,746	337,105
Loss from operations	(939,431)	(814,673)	(500,088)	(424,587)	(296,008)
Net loss	$ (886,116)	$ (761,497)	$ (490,874)	$ (410,108)	$ (290,073)
Net loss per common share — basic and diluted	$ (8.11)	$ (7.57)	$ (5.42)	$ (4.79)	$ (3.45)
Weighted-average common shares outstanding — basic and diluted	109,264	100,590	90,554	85,596	83,992
(1) Stock-based compensation expenses included in operating costs and expenses	$ 174,841	$ 157,752	$ 92,819	$ 75,528	$ 45,783

(2) 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,				
	2019	2018	2017	2016 (1)	2015 (1)
Balance Sheet Data:					
Cash, cash equivalents and marketable debt and equity securities	$ 1,536,162	$ 1,084,155	$ 1,704,537	$ 942,601	$ 1,280,951
Restricted investments	14,825	44,825	30,000	150,000	—
Working capital	1,363,270	1,021,202	1,620,489	540,178	1,043,289
Total assets	2,395,134	1,574,802	1,994,730	1,262,810	1,386,510
Long-term debt	—	30,000	30,000	150,000	—
Total stockholders' equity	1,438,692	1,301,965	1,766,431	920,221	1,264,714

(1) Excluding our investment in equity securities of Regulus Therapeutics, Inc.

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Overview

We are a global commercial-stage biopharmaceutical company that discovers, develops, manufactures and commercializes novel therapeutics based on RNAi. Our commercialized products and broad pipeline of investigational RNAi therapeutics are focused in four STArs: Genetic Medicines, Cardio-Metabolic Diseases, Hepatic Infectious Diseases and CNS/Ocular Diseases.

As described in Part I, Item 1. "Business," of this annual report on Form 10-K, we currently have two products that have received marketing approval and six late-stage investigational programs advancing towards potential commercialization. Also refer to Part I, Item 1. "Business" for a summary of key events in 2019 and 2020 to-date related to our marketed products and our clinical development programs.

We have incurred significant losses since we commenced operations in 2002 and expect such losses to continue for the foreseeable future. As of December 31, 2019, we had an accumulated deficit of $3.73 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 commercial 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 in August 2018 received regulatory approval from the FDA and EC for our first product, ONPATTRO, and began to generate net revenues from product sales during the third quarter of 2018. Furthermore, in November 2019 we received FDA approval for our second product, GIVLAARI, and began to generate net revenues from product sales during the fourth quarter of 2019. 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, GIVLAARI 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 Regeneron, Sanofi Genzyme and MDCO. In addition to revenues from the commercial sales of ONPATTRO, GIVLAARI 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, as well as proceeds from the sale of equity or debt.

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:

Net Product Revenues

Our net product sales consist of sales of ONPATTRO and GIVLAARI and are recognized, net of variable consideration related to certain allowances and accruals, at the time the customer obtains control of our product. We use the expected value method, which is the sum of probability-weighted amounts in a range of possible consideration amounts, or the most likely amount method, which is the single most likely amount in a range of possible considerations, to estimate variable consideration related to our product sales. We use the expected value method to estimate variable consideration for certain rebates, chargebacks, product returns, and other incentives and we use the most likely amount method for certain rebates and trade discounts and allowances.

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 customer who directly purchases from us. The customer charges us for the difference between what it 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 other countries, including countries in which we are accruing for estimated rebates because final pricing has not yet been negotiated. We are also subject to potential rebates in connection with our VBAs with certain commercial payors. We record reserves for rebates in the same period the related product revenue is recognized, resulting in a reduction of 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, expected utilization or an estimated number of patients on treatment, as applicable.

Trade discounts and allowances: We provide customary invoice discounts on product 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 product revenues and accounts receivable at the time we recognize the related revenues.

Product returns: We offer customers product return rights if products are damaged, defective or expired, with “expired” defined as within three months pre- or post-expiry. We estimate the amount of product that will be returned using a probability-weighted estimate based on our sales history.

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 our products based on expected customer demographics and record any such amounts within accrued expenses on our consolidated balance sheet.

Revenues from Collaborators

We earn revenue in connection with collaboration agreements which allow our collaboration partners to utilize our technology platforms and develop product candidates. Our collaboration agreements are detailed in Note 4, Collaboration 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. For each collaboration partner, we discuss our revenue recognition, including our significant performance obligations under each agreement.

At contract inception, we assess whether the collaboration arrangements are within the scope of Accounting Standards Codification, or ASC, Topic 808, Collaborative Arrangements, or ASC 808, to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed based on the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the arrangement are within the scope of ASC 808 and which elements are within the scope of ASC Topic 606, Revenue from Contracts with Customers, or ASC 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, either by analogy to authoritative accounting literature or by applying a reasonable and rational policy election.

For elements of collaboration arrangements that are accounted for pursuant to ASC 606, we identify the performance obligations and allocate the total consideration we expect to receive on a relative standalone selling price basis to each performance obligation. Variable consideration such as performance-based milestones will be included in the total consideration if we expect to receive such consideration and if it is probable that the inclusion of the variable consideration will not result in a significant reversal in the cumulative amount of revenue recognized under the arrangement. Our estimate of the total consideration we expect to receive under each collaboration arrangement is updated for each reporting period, and any adjustments to revenue are recorded on a cumulative catch-up basis. We exclude sales-based royalty and milestone payments from the total consideration we expect to receive until the underlying sales occur because the license to our intellectual property is deemed to be the predominant item to which the royalties or milestones relate as it is the primary driver of value in our collaboration arrangements.

Key assumptions to determine the standalone selling price may include forecasted revenues, development timelines, reimbursement rates for personnel costs, the expected number of targets or indications expected to be pursued under each license, discount rates and probabilities of technical and regulatory success. We recognize revenue associated with each performance obligation as the control over the promised goods or services transfer to our collaboration partner which occurs either at a point in time or over time. If control transfers over time, revenue is recognized by using a method of measuring progress that best depicts the transfer of goods or services. We evaluate the measure of progress and related inputs each reporting period and any resulting adjustments to revenue are recorded on a cumulative catch-up basis.

Consideration received that does not meet the requirements to satisfy ASC 808 or ASC 606 revenue recognition criteria is recorded as deferred revenue in the accompanying consolidated balance sheets, classified as either short-term or long-term deferred revenue based on our best estimate of when, less than 12 months (short-term) or more than 12 months (long-term), such revenue will be recognized.

Inventory

We capitalize inventory costs that are expected to be sold commercially once we determine it is probable 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 received, considering any special filing status, (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) current market factors, including competitive landscape and pricing, (vi) threatened or anticipated litigation challenges, (vii) history of approvals of similar products or formulations and (viii) FDA (or other appropriate regulatory agencies) correspondence regarding the safety and efficacy of the product. Prior to the capitalization of inventory costs, we record such costs as research and development expenses on our consolidated statements of operations and comprehensive loss.

On a quarterly basis, we evaluate the recoverability of capitalized inventory using significant judgments, estimates and assumptions, primarily those related to commercial sales forecasts and product shelf life. We periodically review inventory levels to identify what may expire prior to expected sale or has a cost basis in excess of its estimated realizable value. We write-down such inventories as appropriate.

Income Taxes

Uncertain tax positions, for which management's assessment is that there is a more than 50% probability of sustaining the position upon challenge by a taxing authority based upon its technical merits, are subject to certain recognition and measurement criteria. 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 re-evaluate these uncertain tax positions on a quarterly basis based on a number of 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.

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.

Stock-Based Compensation

We recognize stock-based compensation expense for grants under our stock incentive plans and employee stock purchase plan, as well as inducement stock grants outside of our stock incentive plans. We account for all stock-based awards granted to employees at their fair value and 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, which requires the input of subjective assumptions, including but not limited to expected stock price volatility over the term of the awards and the expected term of stock options. 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.

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, a determination which 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.

Research and Development Accruals

We record accrued liabilities related to products we have received or services that we have incurred, specifically related to ongoing pre-clinical studies and clinical trials, for which service providers have not yet billed us, or when billing terms under these contracts do not coincide with the timing of when the work is performed, as of our period-end. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator fees. The assessment of these costs is a subjective process, requiring judgment based on our knowledge of the research and development programs, services performed for the period, experience with related activities and the expected duration of the third-party service contract, where applicable. 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, in thousands:

	Year Ended December 31,		
Description	**2019**	**2018**	**2017 [1]**
Revenues	$ 219,750	$ 74,908	$ 89,912
Operating costs and expenses	$ 1,159,181	$ 889,581	$ 590,000
Loss from operations	$ (939,431)	$ (814,673)	$ (500,088)
Net loss	$ (886,116)	$ (761,497)	$ (490,874)

[1] Periods prior to our adoption of ASC 606 have not been adjusted under the modified retrospective method. 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.

For discussion of our 2018 results and a comparison with 2017 results please refer to "Management's Discussion and Analysis of Financial Conditions and Results of Operations" in our Annual Report on Form 10-K for the fiscal year ended December 31, 2018.

Revenues

The following table summarizes our total consolidated revenues, in thousands:

Description	Years Ended December 31, 2019	2018	2017 [1]	2019 vs 2018 Dollar Change	2019 vs 2018 Percent Change	2018 vs 2017 Dollar Change	2018 vs 2017 Percent Change
Net product revenues	$ 166,537	$ 12,535	$ —	$ 154,002	1229 %	$ 12,535	N/A
Net revenues from collaborators	53,213	62,373	89,912	(9,160)	(15)%	(27,539)	(31)%
Total	$ 219,750	$ 74,908	$ 89,912	$ 144,842	193 %	$ (15,004)	(17)%

[1] As noted above, prior period amounts have not been adjusted under the modified retrospective method.

Net Product Revenues

We began to record net product revenues following regulatory approval of ONPATTRO and its subsequent commercial launch in the U.S. and several countries in Europe during the third and fourth quarters of 2018, respectively. Net product sales increased during the year ended December 31, 2019, compared to the year ended December 31, 2018, as a result of an entire year of ONPATTRO sales activities and continued expansion into additional major markets. In November 2019, we received FDA approval for GIVLAARI and in December 2019, we commercially launched GIVLAARI in the U.S.

Net product revenues consist of the following, in thousands:

Description	Years Ended December 31, 2019	2018	2017	2019 vs 2018 Dollar Change	2019 vs 2018 Percent Change	2018 vs 2017 Dollar Change	2018 vs 2017 Percent Change
United States	$ 116,452	$ 8,589	$ —	$ 107,863	1256 %	$ 8,589	N/A
Rest of World	50,085	3,946	—	46,139	1169 %	3,946	N/A
Total net product revenues	$ 166,537	$ 12,535	$ —	$ 154,002	1229 %	$ 12,535	N/A

We expect net product revenues to increase during 2020 as compared to 2019 as we continue to add new patients onto ONPATTRO and GIVLAARI therapy, as well as launch our approved products into additional markets, assuming regulatory approvals.

Please read Note 3 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 balances and activity in each product revenue allowance and reserve category for the years ended December 31, 2019 and 2018.

Net Revenues from Collaborators

The following table summarizes our total consolidated net revenues from collaborators under our research and development collaborations, in thousands:

Description	Years Ended December 31, 2019	2018	2017 [1]	2019 vs 2018 Dollar Change	2019 vs 2018 Percent Change	2018 vs 2017 Dollar Change	2018 vs 2017 Percent Change
Regeneron Pharmaceuticals	$ 26,075	$ —	$ —	$ 26,075	N/A	$ —	N/A
Vir Biotechnology	12,809	12,778	1,464	31	— %	11,314	773 %
Sanofi Genzyme	10,976	46,000	54,625	(35,024)	(76)%	(8,625)	(16)%
The Medicines Company	2,315	2,789	30,217	(474)	(17)%	(27,428)	(91)%
Other	1,038	806	3,606	232	29 %	(2,800)	(78)%
Total	$ 53,213	$ 62,373	$ 89,912	$ (9,160)	(15)%	$ (27,539)	(31)%

[1] As noted above, prior period amounts have not been adjusted under the modified retrospective method.

Net revenues from collaborators decreased during the year ended December 31, 2019, as compared to the year ended December 31, 2018, primarily due to a decrease in reimbursable activities in connection with our collaboration agreements with Sanofi Genzyme, offset by an increase in revenues in connection with our collaboration agreement with Regeneron.

We expect net revenues from collaborators to increase during 2020 as compared to 2019 due primarily to increased reimbursable activities and milestones under our existing collaborations, as well as an increase in revenues in connection with our collaboration with Regeneron.

Operating Costs and Expenses

The following table summarizes our operating costs and expenses, in thousands:

	Year Ended December 31,			2019 vs 2018		2018 vs 2017	
Description	**2019**	**2018**	**2017**	**Dollar Change**	**Percent Change**	**Dollar Change**	**Percent Change**
Cost of goods sold	$ 25,062	$ 1,802	$ —	$ 23,260	1291 %	$ 1,802	N/A
Research and development	655,114	505,420	390,635	149,694	30 %	114,785	29 %
Selling, general and administrative	479,005	382,359	199,365	96,646	25 %	182,994	92 %
Total	$ 1,159,181	$ 889,581	$ 590,000	$ 269,600	30 %	$ 299,581	51 %

Cost of Goods Sold

Cost of goods sold includes the cost of producing and distributing inventories that are related to product revenues, third-party royalties, and amortization of licensing rights. Cost of goods sold increased during the year ended December 31, 2019, as compared to the year ended December 31, 2018, primarily due to the increase in net product revenues and a charge for excess and obsolete ONPATTRO inventories. Based on our policy, we record costs associated with the manufacturing of our products as research and development expense prior to FDA approval or until we expect that these costs will be recoverable through commercialization of our products (zero-cost inventory). Certain units of product sold and recognized as revenue during the years ended December 31, 2019 and 2018 were zero-cost inventory and therefore the cost of goods sold for the years ended December 31, 2019 and 2018 reflects only a portion of the manufacturing cost of our commercial products. As of December 31, 2019, we had sold substantially all zero-cost inventory of ONPATTRO. We will continue to sell our zero-cost inventory of GIVLAARI in 2020. We anticipate variability in our cost of goods sold as a percentage of net product revenues due to the timing of manufacturing runs and utilization and the depletion of zero-cost inventories, as well as future product launches.

We expect that cost of goods sold will increase during 2020 as compared to 2019 primarily as a result of an expected increase in net product sales.

Research and Development

The following table summarizes the components of our research and development expenses, in thousands:

	Year Ended December 31,			2019 vs 2018		2018 vs 2017	
Description	**2019**	**2018**	**2017**	**Dollar Change**	**Percent Change**	**Dollar Change**	**Percent Change**
Clinical trial and manufacturing	$ 203,897	$ 173,271	$ 142,411	$ 30,626	18 %	$ 30,860	22 %
Compensation and related	157,001	116,350	100,728	40,651	35 %	15,622	16 %
Stock-based compensation	88,930	80,509	51,872	8,421	10 %	28,637	55 %
External services	75,448	55,165	38,675	20,283	37 %	16,490	43 %
Facilities-related	54,650	42,159	31,022	12,491	30 %	11,137	36 %
License fees	37,030	7,959	7,651	29,071	365 %	308	4 %
Lab supplies, materials and other	38,158	30,007	18,276	8,151	27 %	11,731	64 %
Total	$ 655,114	$ 505,420	$ 390,635	$ 149,694	30 %	$ 114,785	29 %

Research and development expenses increased during the year ended December 31, 2019, as compared to the year ended December 31, 2018, primarily due to the following:

- Increased clinical trial and manufacturing and external services expenses as a result of increased pre-clinical and clinical services related to the advancement of our early and late-stage programs to support our long-term strategic goals;
- Increased compensation and related expenses and facilities-related expenses, as a result of growth in headcount to support our goals for 2020; and
- Increased license fees resulting from our collaboration agreement with Regeneron.

During the years ended December 31, 2019 and 2018, in connection with advancing activities under our collaboration agreements, we incurred research and development expenses, primarily related to external development and manufacturing

services. The following table summarizes the expenses incurred, for which we recognize net revenue, under our collaboration agreements by collaboration partner, in thousands:

	Year Ended December 31,		
Description	**2019**	**2018**	**2017**
Regeneron Pharmaceuticals	$ 24,916	$ —	$ —
Vir Biotechnology	15,479	16,071	2,060
Sanofi Genzyme	13,856	43,219	184,703
The Medicines Company	2,721	1,869	5,527
Ionis Pharmaceuticals	—	3,247	3,250
Total	$ 56,972	$ 64,406	$ 195,540

We expect to continue to devote a substantial portion of our resources to research and development expenses to support our long-term strategic goals. We expect that research and development expenses will increase during 2020 as compared to 2019 as we continue to develop our pipeline and advance our product candidates, including partnered programs, 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.

Selling, General and Administrative

The following table summarizes the components of our selling, general and administrative expenses, in thousands:

	Year Ended December 31,			2019 vs 2018		2018 vs 2017	
Description	**2019**	**2018**	**2017**	**Dollar Change**	**Percent Change**	**Dollar Change**	**Percent Change**
Consulting and professional services	$ 155,843	$ 137,201	$ 68,847	$ 18,642	14 %	$ 68,354	99 %
Compensation and related	148,271	107,376	60,289	40,895	38 %	47,087	78 %
Stock-based compensation	85,911	77,243	40,947	8,668	11 %	36,296	89 %
Facilities-related	35,779	25,658	11,130	10,121	39 %	14,528	131 %
Other	53,201	34,881	18,152	18,320	53 %	16,729	92 %
Total	$ 479,005	$ 382,359	$ 199,365	$ 96,646	25 %	$ 182,994	92 %

Selling, general and administrative expenses increased during the year ended December 31, 2019, as compared to the year ended December 31, 2018, primarily due to the following:

- Increased compensation and related, consulting and professional services, and facilities-related expenses, as a result of increased commercial and medical affairs headcount and increased commercial-related services to support long-term strategic goals, the continued expansion of ONPATTRO into additional major markets, and the launch of GIVLAARI in December 2019.

We expect that selling, general and administrative expenses will increase during 2020 as compared to 2019 as we continue to grow our operations, including the continued build-out of our global commercial infrastructure and field team to support ONPATTRO, GIVLAARI 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.

Liquidity and Capital Resources

Overview

Since we commenced operations in 2002, we have generated significant losses. As of December 31, 2019, we had an accumulated deficit of $3.73 billion. As of December 31, 2019, we had cash, cash equivalents and marketable debt and equity securities of $1.54 billion, compared to $1.08 billion as of December 31, 2018.

We have required significant amounts of cash to fund our operating activities as a result of net losses since our inception and we expect that we will continue to require significant amounts of cash to fund our operating activities for the foreseeable future as we continue to execute on our long-term strategic goals 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 net product revenues and 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 following table summarizes our cash flow activities, in thousands:

	Year Ended December 31,		
	2019	2018	2017
Net loss	$ (886,116)	$ (761,497)	$ (490,874)
Non-cash adjustments to reconcile net loss to net cash used in operating activities:	205,308	153,782	110,990
Changes in operating assets and liabilities:	402,381	45,099	(2,902)
Net cash used in operating activities	(278,427)	(562,616)	(382,786)
Net cash (used in) provided by investing activities	(417,677)	272,945	(290,361)
Net cash provided by financing activities	823,184	65,470	1,124,891
Effect of exchange rate changes on cash, cash equivalents and restricted cash	(83)	—	—
Net increase (decrease) in cash, cash equivalents and restricted cash	126,997	(224,201)	451,744
Cash, cash equivalents and restricted cash, beginning of period	422,631	646,832	195,088
Cash, cash equivalents and restricted cash, end of period	$ 549,628	$ 422,631	$ 646,832

Operating Activities

Net cash used in operating activities decreased during the year ended December 31, 2019, compared to the year ended December 31, 2018, primarily due to the increase of deferred revenue associated with consideration of $400.0 million received under our strategic collaboration with Regeneron in May 2019, partially offset by an increase in our net loss attributable to increased operating expenses to support overall growth.

Investing Activities

Net cash used in investing activities increased during the year ended December 31, 2019, compared to the year ended December 31, 2018, primarily due to net activities related to our marketable debt securities, partially offset from cash provided by proceeds of $30.0 million from the release of our restricted cash collateral in connection with termination of our outstanding credit agreement.

Financing Activities

Net cash provided by financing activities increased during the year ended December 31, 2019, compared to the year ended December 31, 2018, primarily due to proceeds of $400.0 million received from our issuance of common stock to Regeneron and aggregate net proceeds of $381.9 million received from our January 2019 underwritten public offering.

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. In November 2019, we received FDA approval for our second product, GIVLAARI, and launched the product in the U.S. in December 2019. 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.

Based on our current operating plan, we believe that our cash, cash equivalents and marketable debt and equity securities as of December 31, 2019, together with the cash we expect to generate from product sales and under our current alliances, including our 2019 collaboration with Regeneron, will be sufficient to enable us to advance our long-term strategic goals for at least the next 12 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 GIVLAARI, 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, public or private equity offerings or debt financings, or a combination of one or more of these funding sources. Additional funding may not be available to us on acceptable terms or at all. Moreover, the terms of any additional 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 funds to us, future investors may demand, and may be granted, rights superior to those of existing stockholders. Moreover, any debt financing, if available, may involve restrictive covenants that could limit our flexibility in conducting future business activities and, in the event of insolvency, would be paid before holders of equity securities received any distribution of corporate assets. If an event of default were to occur under any such financing, the interest rate could increase and the lenders could be entitled to take various actions, including the acceleration of amounts due under the loan. Our ability to satisfy and meet any future 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.

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 long-term strategic goals 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, GIVLAARI and our other potential products.

Off-Balance Sheet Arrangements

In connection with license agreements we may enter with companies to obtain rights to intellectual property, we may be required to indemnify such companies for certain damages arising in connection with the intellectual property rights licensed under the agreements. Under such indemnification agreements we may be 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 licensed intellectual property. 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, including litigation. For example, under the underwriting agreement entered into in connection with our November 2017 public offering, we have an obligation to indemnify the underwriters and each person, if any, who controls the underwriters, for certain costs and expenses arising in connection with the class action complaint filed against us and such underwriters in New York state court. These indemnification costs are charged to selling, general and administrative expense and are considered off-balance sheet arrangements in accordance with GAAP. To date, other than certain costs associated with certain previously settled 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.

Contractual Obligations

In the table below, we set forth our enforceable and legally binding obligations and future commitments as of December 31, 2019. Some of the figures that we include in this table are based on management’s estimates and assumptions about these obligations, including their duration, the possibility of renewal, anticipated actions by third parties and other factors.

Because these estimates and assumptions are necessarily subjective, the obligations we will actually pay in future periods may vary from those reflected in the table.

	Payments Due by Period				
Contractual Obligations	**2020**	**2021 and 2022**	**2023 and 2024**	**After 2024**	**Total**
Facility lease obligations (1)	$ 29,157	$ 75,351	$ 71,631	$ 356,567	$ 532,706
Technology license commitments (2)	795	1,290	600	—	2,685
Total contractual cash obligations	$ 29,952	$ 76,641	$ 72,231	$ 356,567	$ 535,391

(1) Relates primarily to our Cambridge, Massachusetts non-cancelable facility lease agreements.
(2) Relates to our fixed payment obligations under license agreements.

The table above excludes approximately $441.2 million of commitments related to clinical and manufacturing-related agreements and approximately $13.6 million of commitments related to manufacturing-related agreements executed in January 2020, as they are cancellable. We in-license technology from a number of sources, including Ionis and Merck. 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 sales of our approved products. 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, during the next 12 months from the filing of this annual report on Form 10-K, potential milestone payments due to third parties, could be approximately $18.4 million, including $12.8 million in regulatory and development milestones and $5.6 million in commercial milestones, in connection with our various collaborations and license agreements. These milestones generally become due and payable upon achievement. Because the achievement of these milestones was not considered probable as of December 31, 2019, 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

Interest Rate Risk - Investment Portfolio. We invest a portion of our cash in a number of diversified fixed- and floating-rate securities consisting of cash equivalents, marketable debt securities, debt funds and derivative instruments related to our investment portfolio that are subject to interest rate risk. Changes in the general level of interest rates can affect the fair value of our investment portfolio. If interest rates in the general economy were to rise, our holdings could lose value. As of December 31, 2019 and 2018, a hypothetical increase in interest rates of 50 basis points across the entire yield curve on our holdings would have resulted in an immaterial decrease to the fair value of our holdings.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

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, 2019 and 2018, and the related consolidated statements of operations and comprehensive loss, of stockholders' equity and of cash flows for each of the three years in the period ended December 31, 2019, 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, 2019, 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, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019 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, 2019, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

Changes in Accounting Principles

As discussed in Note 2 to the consolidated financial statements, the Company changed the manner in which it accounts for leases in 2019 and 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 Management's Annual Report on Internal Control over Financial Reporting appearing under Item 9A. 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.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Regeneron Collaboration Determination of Standalone Selling Price

As described in Note 4 to the consolidated financial statements, the Company entered into a collaboration with Regeneron Pharmaceuticals, Inc. (the "Regeneron Collaboration") in 2019. The Company's obligations under the Regeneron Collaboration include: (i) a research license and research services, collectively referred to as the Research Services Obligation; (ii) a worldwide license to cemdisiran for combination therapies, and manufacturing and supply, and development service obligations, collectively referred to as the C5 License Obligation; and (iii) development, manufacturing and commercialization activities for cemdisiran monotherapies, referred to as the C5 Co-Co Obligation. The initial transaction price of $521.6 million was allocated to the obligations based on the relative estimated standalone selling prices of each obligation, over which management has applied significant judgment. Management developed the estimated standalone selling price for the licenses included in the Research Services Obligation and the C5 License Obligation primarily based on the probability-weighted present value of expected future cash flows associated with each license related to each specific program. In developing this estimate, management applied judgment in the determination of the forecasted revenues, taking into consideration the applicable market conditions and relevant entity-specific factors, the expected number of targets or indications expected to be pursued under each license, the probability of success, the time needed to develop a product candidate pursuant to the associated license and the discount rate. Management developed the estimated standalone selling price for the services and/or manufacturing and supply included in each of the obligations, as applicable, primarily based on the nature of the services to be performed and/or goods to be manufactured and estimates of the associated costs. The estimated standalone selling price of the C5 Co-Co Obligation was developed by estimating the present value of expected future cash flows that Regeneron is entitled to receive. In developing this estimate, management applied judgment in determining the indications that will be pursued, the forecasted revenues for such indications, the probability of success, and the discount rate.

The principal considerations for our determination that performing procedures relating to the Regeneron Collaboration determination of the standalone selling price is a critical audit matter are there was significant judgment by management in developing the estimates of standalone selling price, as the estimates are based on a number of assumptions, including the indications that will be pursued, the forecasted revenues for such indications, the probability of success, the discount rate, and estimates for manufacturing and supply costs. This in turn led to a high degree of auditor judgment, effort and subjectivity in performing procedures relating to the assumptions used by management in developing the estimates of standalone selling price. In addition, the audit effort involved the use of professionals with specialized skill and knowledge to assist in evaluating the audit evidence obtained.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls relating to the estimation of the standalone selling price, including controls over the review of the methods used to develop standalone selling price, and controls over development of the assumptions related to the methods, including expected future cash flows, discount rates, probability of success and costs estimates for manufacturing and supply costs. These procedures also included, among others, reading the contractual terms of the collaboration arrangement, understanding and testing management's process for developing the standalone selling price, including evaluating the appropriateness of the method and the reasonableness of management's assumptions relating to the indications that will be pursued, forecasted future revenues, probability of success, and estimates for manufacturing and supply costs, and testing the completeness, accuracy, and relevance of underlying data used. Evaluating management's assumptions related to the future revenue included in the expected future cash flows, probability of success, and cost estimates for manufacturing and supply costs involved evaluating whether the assumptions used by management were reasonable considering the consistency with data from internal and external sources including market and industry data, and performance of the clinical programs since inception of the collaboration. Professionals with specialized skill and knowledge were used to assist in the evaluation of the Company's methods for determining the standalone selling price and certain assumptions in those methods, including the discount rate.

/s/PricewaterhouseCoopers LLP
Boston, Massachusetts
February 13, 2020

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

ALNYLAM PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except per share amounts)

	December 31, 2019	December 31, 2018
ASSETS		
Current assets:		
Cash and cash equivalents	$ 547,178	$ 420,146
Marketable debt securities	975,017	662,803
Marketable equity securities	13,967	1,206
Accounts receivable, net	43,011	18,760
Inventory	56,348	24,068
Prepaid expenses and other current assets	80,343	73,713
Total current assets	1,715,864	1,200,696
Property, plant and equipment, net	425,179	320,658
Operating lease right-of-use assets	221,197	—
Restricted investments	14,825	44,825
Other assets	18,069	8,623
Total assets	$ 2,395,134	$ 1,574,802
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 49,884	$ 59,708
Accrued expenses	197,201	112,719
Operating lease liability	27,688	—
Deferred rent	—	3,571
Deferred revenue	77,821	3,496
Total current liabilities	352,594	179,494
Operating lease liability, net of current portion	276,135	—
Deferred rent, net of current portion	—	57,920
Deferred revenue, net of current portion	318,383	458
Long-term debt	—	30,000
Other liabilities	9,330	4,965
Total liabilities	956,442	272,837
Commitments and contingencies (Note 9)		
Stockholders' equity:		
Preferred stock, $0.01 par value per share, 5,000 shares authorized and no shares issued and outstanding as of December 31, 2019 and December 31, 2018	—	—
Common stock, $0.01 par value per share, 250,000 and 125,000 shares authorized as of December 31, 2019 and December 31, 2018, respectively; 112,188 shares issued and outstanding as of December 31, 2019; 101,177 shares issued and outstanding as of December 31, 2018	1,122	1,011
Additional paid-in capital	5,201,176	4,175,139
Accumulated other comprehensive loss	(36,518)	(33,213)
Accumulated deficit	(3,727,088)	(2,840,972)
Total stockholders' equity	1,438,692	1,301,965
Total liabilities and stockholders' equity	$ 2,395,134	$ 1,574,802

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

ALNYLAM PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except per share amounts)

	Year Ended December 31,		
	2019	2018	2017
Statements of Operations			
Revenues:			
Net product revenues	$ 166,537	$ 12,535	$ —
Net revenues from collaborators	53,213	62,373	89,912
Total revenues	219,750	74,908	89,912
Operating costs and expenses:			
Cost of goods sold	25,062	1,802	—
Research and development	655,114	505,420	390,635
Selling, general and administrative	479,005	382,359	199,365
Total operating costs and expenses	1,159,181	889,581	590,000
Loss from operations	(939,431)	(814,673)	(500,088)
Other income (expense):			
Interest income	33,448	29,262	12,236
Other income (expense)	11,308	4,173	(3,022)
Change in fair value of liability obligation	9,422	—	—
Gain on litigation settlement	—	20,564	—
Total other income	54,178	53,999	9,214
Loss before income taxes	(885,253)	(760,674)	(490,874)
Provision for income taxes	(863)	(823)	—
Net loss	$ (886,116)	$ (761,497)	$ (490,874)
Net loss per common share — basic and diluted	$ (8.11)	$ (7.57)	$ (5.42)
Weighted-average common shares used to compute basic and diluted net loss per common share	109,264	100,590	90,554
Statements of Comprehensive Loss			
Net loss	$ (886,116)	$ (761,497)	$ (490,874)
Other comprehensive (loss) income, net of tax:			
Unrealized gain (loss) on marketable securities	558	1,220	(2,886)
Foreign currency translations	(343)	—	—
Defined benefit pension plans	(3,520)	—	—
Reclassification adjustment for realized loss on marketable securities included in net loss	—	—	1,894
Comprehensive loss	$ (889,421)	$ (760,277)	$ (491,866)

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 Other Comprehensive (Loss) Income	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance as of December 31, 2016	85,941	$ 859	$ 2,609,614	$ (33,441)	$ (1,656,811)	$ 920,221
Exercise of common stock options	1,842	19	80,527	—	—	80,546
Issuance of common stock under equity plans	115	1	3,159	—	—	3,160
Issuance of common stock under benefit plans	31	1	2,039	—	—	2,040
Issuance of common stock to Sanofi Genzyme	298	3	21,378	—	—	21,381
Issuance of common stock, net of offering costs	11,440	114	1,139,511	—	—	1,139,625
Stock-based compensation expense related to equity-classified awards	—	—	91,324	—	—	91,324
Other comprehensive loss, net of tax	—	—	—	(992)	—	(992)
Net loss	—	—	—	—	(490,874)	(490,874)
Balance as of December 31, 2017	99,667	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	1,268	12	60,731	—	—	60,743
Issuance of common stock under equity plans	212	2	5,044	—	—	5,046
Issuance of common stock under benefit plans	30	—	3,170	—	—	3,170
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 as of December 31, 2018	101,177	1,011	4,175,139	(33,213)	(2,840,972)	1,301,965
Exercise of common stock options, net of tax withholdings	1,374	15	63,484	—	—	63,499
Issuance of common stock under equity plans	132	1	7,908	—	—	7,909
Issuance of common stock under benefit plans	61	1	5,032	—	—	5,033
Issuance of common stock, net of offering costs	9,444	94	772,383	—	—	772,477
Stock-based compensation expense related to equity-classified awards	—	—	177,230	—	—	177,230
Other comprehensive loss, net of tax	—	—	—	(3,305)	—	(3,305)
Net loss	—	—	—	—	(886,116)	(886,116)
Balance as of December 31, 2019	112,188	$ 1,122	$ 5,201,176	$ (36,518)	$ (3,727,088)	$ 1,438,692

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,		
	2019	**2018**	**2017**
Cash flows from operating activities:			
Net loss	$ (886,116)	$ (761,497)	$ (490,874)
Non-cash adjustments to reconcile net loss to net cash used in operating activities:			
Amortization and interest accretion related to operating leases	37,193	—	—
Depreciation and amortization	17,175	15,248	11,898
Stock-based compensation	174,841	157,752	92,819
Gain on litigation settlement	—	(10,000)	—
Fair value adjustments on marketable equity securities	(11,288)	(3,564)	1,894
Change in fair value of liability obligation	(9,422)	—	—
Other	(3,191)	(5,654)	4,379
Changes in operating assets and liabilities:			
Proceeds from landlord lease incentive for tenant improvements	30,170	25,350	—
Accounts receivable, net	(24,238)	15,242	(10,668)
Inventory	(32,411)	(22,645)	—
Prepaid expenses and other assets	(22,042)	(35,067)	(20,711)
Accounts payable, accrued expenses and other	92,354	74,835	26,629
Operating lease liability	(33,703)	—	—
Deferred revenue	392,251	(12,616)	1,848
Net cash used in operating activities	(278,427)	(562,616)	(382,786)
Cash flows from investing activities:			
Purchases of property, plant and equipment	(140,156)	(126,887)	(104,209)
Purchases of restricted investments	—	(14,825)	—
Proceeds from maturity of restricted investments	30,000	—	120,000
Purchases of marketable debt securities	(2,075,925)	(1,104,046)	(903,457)
Sales and maturities of marketable debt securities	1,775,404	1,518,703	597,305
Other	(7,000)	—	—
Net cash (used in) provided by investing activities	(417,677)	272,945	(290,361)
Cash flows from financing activities:			
Proceeds from exercise of stock options and other types of equity, net	71,284	65,470	83,885
Offering proceeds, net of costs	381,900	—	1,139,625
Proceeds from issuance of common stock to Sanofi Genzyme	—	—	21,381
Repayment of term loan	(30,000)	—	(120,000)
Proceeds from issuance of common stock to Regeneron	400,000	—	—
Net cash provided by financing activities	823,184	65,470	1,124,891
Effect of exchange rate changes on cash, cash equivalents and restricted cash	(83)	—	—
Net increase (decrease) in cash, cash equivalents and restricted cash	126,997	(224,201)	451,744
Cash, cash equivalents and restricted cash, beginning of period	422,631	646,832	195,088
Cash, cash equivalents and restricted cash, end of period	$ 549,628	$ 422,631	$ 646,832
Supplemental disclosure of cash flows:			
Cash paid for interest	$ 172	$ 775	$ 2,430
Cash paid for income taxes	$ 2,566	$ 1,066	$ 114
Supplemental disclosure of noncash investing and financing activities:			
Capital expenditures included in accounts payable and accrued expenses	$ 14,876	$ 33,274	$ 8,176

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

1. NATURE OF BUSINESS

Alnylam Pharmaceuticals, Inc. (also referred to as Alnylam, we, our or us) 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, global, commercial biopharmaceutical company with a deep and sustainable clinical pipeline of RNAi therapeutics for future growth and a robust, organic research engine for sustainable innovation and great potential for patient impact. 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 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. As of December 31, 2019, we have launched ONPATTRO in the U.S., Japan, Canada and in several countries in Europe. In November 2019, we received approval for GIVLAARI from the FDA and began commercializing and generating product revenues in the U.S. in December 2019. Regulatory filings in additional markets are pending or planned for 2020 and beyond for both commercial products.

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.

Reclassification

Certain prior period amounts in the consolidated financial statements have been reclassified to conform to the current period presentation.

Liquidity

Based on our current operating plan, we believe that our cash, cash equivalents and marketable debt and equity securities as of December 31, 2019, 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 long-term strategic goals 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. As of December 31, 2019 and 2018, 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.

During the years ended December 31, 2019 and 2018, our revenues were generated primarily from distributors for product sales and collaborations with strategic partners. For the years ended December 31, 2019 and 2018, our gross accounts receivable balance was comprised of payments primarily due from distributors for product sales and our strategic partners.

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

	Year Ended December 31, 2019		
	2019	2018	2017
Distributor A	44 %	13 %	N/A
Sanofi Genzyme	*	58 %	61 %
Vir Biotechnology	*	16 %	*
The Medicines Company	*	*	34 %

* Represents less than 10%

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

	As of December 31, 2019	
	2019	2018
Distributor A	28 %	44 %
Sanofi Genzyme	14 %	29 %
Vir Biotechnology	13 %	*
Distributor B	10 %	*

* Represents less than 10%

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 marketable debt securities and classify our investments 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 and as current assets as they represent the investment of funds available for current operations. 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 (loss) income, a component of stockholders' equity. Realized gains and losses are determined using the specific identification method and are included in other income (expense). 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 operations and comprehensive loss. We did not record any impairment charges related to our marketable debt securities during the years ended December 31, 2019, 2018 or 2017. 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.

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 operations and comprehensive loss. 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. For our marketable debt securities, we perform our own review of prices received from the independent pricing services by comparing these prices to other sources and for our marketable equity securities, we confirm those securities are trading in active markets. 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.

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, 2019 and 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 90 days. Accounts receivable, net on our consolidated balance sheets also includes billed and unbilled collaboration receivables.

Inventory

Inventory is measured at the lower of cost or estimated net realizable value. We use a standard cost basis, which approximates 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 it is probable 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 received, considering any special filing status, (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) current market factors, including competitive landscape and pricing, (vi) threatened or anticipated litigation challenges, (vii) history of approvals of similar products or formulations and (viii) FDA (or other appropriate regulatory agencies) correspondence regarding the safety and efficacy of the product. Prior to the capitalization of inventory costs, we record such costs as research and development expenses on our consolidated statements of operations and comprehensive loss.

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. We periodically review inventory levels to identify what may expire prior to expected sale or has a cost basis in excess of its estimated realizable value and write-down such inventories as appropriate.

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 operations and comprehensive loss. During the years ended December 31, 2019, 2018 and 2017, we recorded $16.6 million, $12.8 million and $11.9 million, respectively, of depreciation expense related to our property, plant and equipment.

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

Asset Category	Useful Life
Laboratory equipment	5
Computer equipment and software	3-10 years
Furniture and fixtures	5
Leasehold improvements	Shorter of asset life or lease term
Manufacturing Equipment	7-15 years
Buildings	40 years
Land	—
Construction in progress	—

Research and Development Accruals

We record accrued liabilities related to products we have received or services that we have incurred, specifically related to ongoing pre-clinical studies and clinical trials, for which service providers have not yet billed us, or when billing terms under these contracts do not coincide with the timing of when the work is performed, as of our period-end. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator fees. The

assessment of these costs is a subjective process, requiring judgment based on our knowledge of the research and development programs, services performed for the period, experience with related activities and the expected duration of the third-party service contract, where applicable. 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 recognize revenue when control of promised goods or services is transferred to a customer at an amount that reflects the consideration to which we expect to be entitled in exchange for those goods or services. To determine revenue recognition, 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, including variable consideration, if any; (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 Accounting Standards Codification Topic 606, Revenue from Contracts with Customers, or ASC 606, 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. As of December 31, 2019 and 2018, we had not capitalized any costs to obtain any of our contracts.

Net Product Revenues

Our net product sales consist of sales of ONPATTRO and GIVLAARI and are recognized, net of variable consideration related to certain allowances and accruals, at the time the customer obtains control of our product. We use the expected value method, which is the sum of probability-weighted amounts in a range of possible consideration amounts, or the most likely amount method, which is the single most likely amount in a range of possible considerations, to estimate variable consideration related to our product sales. We use the expected value method to estimate variable consideration for certain rebates, chargebacks, product returns, and other incentives and we use the most likely amount method for certain rebates and trade discounts and allowances.

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 customer who directly purchases from us. The customer charges us for the difference between what it 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 other countries, including countries in which we are accruing for estimated rebates because final pricing has not yet been negotiated. 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 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, expected utilization or an estimated number of patients on treatment, as applicable.

Trade discounts and allowances: We provide customary invoice discounts on product 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 product revenues and accounts receivable at the time we recognize the related revenues.

Product returns: We offer customers product return rights if products are damaged, defective or expired, with “expired” defined as within three months pre- or post-expiry. We estimate the amount of product that will be returned using a probability-weighted estimate based on our sales history.

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 our products based on expected customer demographics and record any such amounts within accrued expenses on our consolidated balance sheet.

Revenues from Collaborators

We earn revenue in connection with collaboration agreements which allow our collaboration partners to utilize our technology platforms and develop product candidates. Our collaboration agreements are detailed in Note 4, Collaboration Agreements. For each collaboration partner, we discuss our revenue recognition, including our significant performance obligations under each agreement.

At contract inception, we assess whether the collaboration arrangements are within the scope of ASC Topic 808, Collaborative Arrangements, or ASC 808, to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed based on the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the arrangement are within the scope of ASC 808 and which elements are within the scope of ASC 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, either by analogy to authoritative accounting literature or by applying a reasonable and rational policy election.

For elements of collaboration arrangements that are accounted for pursuant to ASC 606, we identify the performance obligations and allocate the total consideration we expect to receive on a relative standalone selling price basis to each performance obligation. Variable consideration such as performance-based milestones will be included in the total consideration if we expect to receive such consideration and if it is probable that the inclusion of the variable consideration will not result in a significant reversal in the cumulative amount of revenue recognized under the arrangement. Our estimate of the total consideration we expect to receive under each collaboration arrangement is updated for each reporting period, and any adjustments to revenue are recorded on a cumulative catch-up basis. We exclude sales-based royalty and milestone payments from the total consideration we expect to receive until the underlying sales occur because the license to our intellectual property is deemed to be the predominant item to which the royalties or milestones relate as it is the primary driver of value in our collaboration arrangements.

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. We recognize revenue associated with each performance obligation as the control over the promised goods or services transfer to our collaboration partner which occurs either at a point in time or over time. If control transfers over time, revenue is recognized by using a method of measuring progress that best depicts the transfer of goods or services. We evaluate the measure of progress and related inputs each reporting period and any resulting adjustments to revenue are recorded on a cumulative catch-up basis.

Consideration received that does not meet the requirements to satisfy ASC 808 or ASC 606 revenue recognition criteria is recorded as deferred revenue in the accompanying consolidated balance sheets, classified as either short-term or long-term deferred revenue based on our best estimate of when, less than 12 months (short-term) or more than 12 months (long-term), such revenue will be recognized.

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 the sale of our products. 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.

Income Taxes

Uncertain tax positions, for which management's assessment is that there is a more than 50% probability of sustaining the position upon challenge by a taxing authority based upon its technical merits, are subject to certain recognition and measurement criteria. 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 re-evaluate these uncertain tax positions on a

quarterly basis based on a number of 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.

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.

As of December 31, 2019, 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, 2019, 2018 and 2017, we charged to research and development expense costs associated with license fees of $37.0 million, $8.0 million and $7.7 million, respectively.

Stock-Based Compensation

We recognize stock-based compensation expense for grants under our stock incentive plans and employee stock purchase plan, as well as 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, which requires the input of subjective assumptions, including but not limited to expected stock price volatility over the term of the awards and the expected term of stock options. 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.

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, a determination which 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. We include certain changes in the fair value of the plan assets and projected benefit obligation attributed to our defined benefit pension plan in other comprehensive loss.

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:

	As of December 31,		
	2019	2018	2017
Options to purchase common stock	13,069	12,573	11,239
Unvested restricted common stock	749	36	149
Total	13,818	12,609	11,388

Segment Information

We operate in a single reporting segment, the discovery, development and commercialization of RNAi therapeutics. Consistent with our management reporting, results of our operations are reported on a consolidated basis for purposes of segment reporting. As of December 31, 2019 and 2018, substantially all of our consolidated property, plant and equipment, net was from U.S. operations. For the years ended December 31, 2019, 2018 and 2017, net revenues from collaborators were attributed to the U.S. Please read Note 3 for information regarding our net product sales by geography.

Recently Adopted Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board, or FASB, issued a new leasing standard, ASC 842, 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 did not restate comparative periods. In addition, we did not elect the package of practical expedients permitted under the transition guidance that permits companies to carry forward prior conclusions related to (1) whether any expired or existing contracts are, or contain, leases, (2) the lease classification for expired or existing leases, and (3) initial direct costs for existing leases. All our leases have been classified as operating leases under the new leasing standard. We elected to combine lease and non-lease components for our facility leases and to keep leases with an initial term of 12 months or less off the consolidated balance sheets and recognize the associated lease payments in the consolidated statements of operations and comprehensive loss on a straight-line basis over the lease term. Please read Note 8 for additional disclosures related to accounting for leases under this new standard.

The adoption of ASC 842 had a material impact on our consolidated balance sheet as the standard requires us to measure and recognize a right of use asset and lease liability. As most leases do not provide an implicit rate, our incremental borrowing rate was determined based on the information available at the date of adoption to measure our lease liability. Costs determined to be variable and not based on an index or rate were not included in the measurement of the lease liability. We recognized approximately $290.0 million of operating lease liabilities and approximately $230.0 million of operating lease right-of-use assets on our consolidated balance sheet as of January 1, 2019. The adoption of the standard did not have a material impact on our consolidated statement of operations and comprehensive loss and there was no impact to cash from or used in operating, financing or investing activities on our consolidated statement of cash flows.

In May 2014, the FASB issued new accounting guidance related to revenue recognition (ASC 606), which outlines a comprehensive revenue recognition model and supersedes most current revenue recognition accounting guidance and requires increased disclosures. The new accounting guidance defines a five-step approach that requires a company to recognize revenue as control of goods or services transfers to a customer at an amount that reflects the expected consideration to be received in exchange for those goods or services. We adopted ASC 606 in the first quarter of 2018 using the modified retrospective method to all contracts that were not completed as of January 1, 2018. We recognized the cumulative effect of initially applying the new revenue accounting guidance as an adjustment to opening retained earnings. Prior period results have not been restated and continue to be reported in accordance with the accounting guidance in effect for those periods.

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:

Consolidated Balance Sheet	Balance as of December 31, 2017	Adjustments	Balance as of January 1, 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. 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.

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 operations and comprehensive loss, in thousands:

	At December 31, 2018		
Consolidated Balance Sheet	**As Reported**	**Balances Without Adoption of New Revenue Standard**	**Effect of Change Higher/(Lower)**
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		
Consolidated Statement of Operations and Comprehensive Loss	**As Reported**	**Balances Without Adoption of New Revenue Standard**	**Effect of Change Higher/(Lower)**
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 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.

Recently Issued Accounting Pronouncements, Not Yet Adopted

In June 2016, the FASB issued new accounting guidance which requires entities to record expected credit losses for certain financial instruments, including trade receivables, as an allowance that reflects the entity's current estimate of credit losses expected to be incurred. For available-for-sale debt securities in unrealized loss positions, the new standard requires allowances to be recorded instead of reducing the amortized cost of the investment. The new standard became effective for us on January 1, 2020. We currently do not expect this guidance to have a significant impact on our consolidated financial statements and related disclosures.

In August 2018, the FASB issued amendments to accounting guidance that eliminate, add and modify certain disclosure requirements on fair value measurements. The new standard became effective for us on January 1, 2020. We currently do not expect this guidance to have a significant impact on our consolidated financial statements and related disclosures.

In August 2018, the FASB issued new accounting guidance to clarify the accounting for implementation costs in cloud computing arrangements (hosting arrangements). The new standard requires a customer in a cloud computing arrangement to determine which implementation costs to capitalize as assets or expense as incurred. Capitalized implementation costs related to a hosting arrangement that is a service contract will be amortized over the term of the hosting arrangement, beginning when the module or component of the hosting arrangement is ready for its intended use. The new standard became effective for us on January 1, 2020. We currently do not expect this guidance to have a significant impact on our consolidated financial statements and related disclosures.

In August 2018, the FASB issued amendments to accounting guidance to modify the disclosure requirements for employers that sponsor a defined benefit pension plan. The amendments become effective for our fiscal year, on a retrospective basis, beginning January 1, 2021, however early adoption is permitted. 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.

In November 2018, the FASB issued new accounting guidance to clarify the interaction between the accounting guidance for collaborative arrangements and revenue from contracts with customers. The new standard became effective for us on January 1, 2020 using a retrospective transition method. We currently do not expect this guidance to have a significant impact on our consolidated financial statements and related disclosures.

In December 2019, the FASB issued amendments to accounting guidance that simplifies the accounting for income taxes, as part of its initiative to reduce complexity in the accounting standards. The amendments eliminate certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. The amendments also clarify and simplify other aspects of the accounting for income taxes. The amendments become effective for our fiscal year, including interim periods, beginning January 1, 2021, however early adoption is permitted. 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 or unrecognized subsequent events.

3. NET PRODUCT REVENUES

Net product revenues by geography consist of the following, in thousands:

	Years Ended December 31,		
	2019	2018	2017
United States	$ 116,452	$ 8,589	$ —
Rest of world	50,085	3,946	—
Total net product revenues	$ 166,537	$ 12,535	$ —

As of December 31, 2019 and 2018, net product revenue-related receivables of $28.1 million and $13.1 million, respectively, were included in “Accounts receivable, net.”

The following table summarizes balances and activity in each product revenue allowance and reserve category during the years ended December 31, 2019 and 2018, in thousands:

	As of December 31, 2019			
	Chargebacks and Rebates	Trade Discounts and Allowances	Returns Reserve and Other Incentives	Total
Beginning balance	$ 3,441	$ 218	$ 321	$ 3,980
Provision related to current period sales	44,371	3,227	5,108	52,706
Credit or payments made during the period for current year sales	(15,216)	(2,817)	(3,231)	(21,264)
Credit or payments made during the period for prior year sales	(109)	(218)	(220)	(547)
Total	$ 32,487	$ 410	$ 1,978	$ 34,875

	As of December 31, 2018			
	Chargebacks and Rebates	Trade Discounts and Allowances	Returns Reserve and Other Incentives	Total
Beginning balance	$ —	$ —	$ —	$ —
Provision related to current period sales	4,081	292	657	5,030
Credit or payments made during the period for current year sales	(640)	(74)	(336)	(1,050)
Total	$ 3,441	$ 218	$ 321	$ 3,980

4. COLLABORATION AGREEMENTS

The following table summarizes our total consolidated net revenues from collaborators, in thousands:

Description	Year Ended December 31, 2019	2018	2017 [1]
Regeneron Pharmaceuticals	$ 26,075	$ —	$ —
Vir Biotechnology	12,809	12,778	1,464
Sanofi Genzyme	10,976	46,000	54,625
The Medicines Company	2,315	2,789	30,217
Other	1,038	806	3,606
Total net revenues from collaborators	$ 53,213	$ 62,373	$ 89,912

[1] As described in Note 2 above, prior period amounts have not been adjusted under the modified retrospective method.

The following table presents the balance of our receivables and contract liabilities related to our collaboration agreements, in thousands:

	As of December 31, 2019	2018
Receivables included in "Accounts receivable, net"	$ 14,929	$ 5,625
Contract liabilities included in "Deferred revenue"	153,117	3,954

The following table presents revenue recognized as a result of changes in contract liability related to our collaboration agreements, in thousands:

	Included in Deferred Revenue
Contract liability as of January 1, 2018	$ 16,570
Consideration earned, not yet recognized as revenue	3,954
Revenue recognized on contract liability as of January 1, 2018	(16,570)
Contract liability as of December 31, 2018	3,954
Consideration earned, not yet recognized as revenue	153,117
Revenue recognized on contract liability as of December 31, 2018	(3,954)
Contract liability as of December 31, 2019	$ 153,117

In order to determine revenue recognized in the period from contract liabilities, we first allocate revenue to the individual contract liability balance outstanding at the beginning of the period until the revenue exceeds that balance. If additional consideration is received on those contracts in subsequent periods, we assume all revenue recognized in the reporting period first applies to the beginning contract liability as opposed to a portion applying to the new consideration for the period.

The following table provides the research and development expenses incurred by type, for which we recognize net revenue, that are directly attributable to our collaboration agreements by collaboration partner, in thousands:

	Year Ended								
	2019			2018			2017		
	Clinical Trial and Manufacturing	External Services	Other	Clinical Trial and Manufacturing	External Services	Other	Clinical Trial and Manufacturing	External Services	Other
Regeneron	$ 2,793	$ 344	$ 21,779	$ —	$ —	$ —	$ —	$ —	$ —
Sanofi	11,505	334	2,017	36,600	5,340	1,279	174,901	4,475	5,327
Vir	10,353	381	4,745	7,272	8,251	548	1,134	926	—
MDCO	2,025	—	696	1,664	2	203	5,421	—	106
Ionis	—	—	—	—	2,150	1,097	—	3,250	—
Total	$ 26,676	$ 1,059	$ 29,237	$ 45,536	$ 15,743	$ 3,127	$ 181,456	$ 8,651	$ 5,433

The research and development expenses incurred for each agreement listed in the table above consist of costs incurred for (i) clinical and manufacturing expenses, (ii) external services including consulting services and lab supplies and services, and

(iii) other expenses, including professional services, facilities and overhead allocations, and a reasonable estimate of compensation and related costs as billed to our counterparties for which we recognize net revenue from collaborations. 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, 2019, 2018 and 2017, we did not incur material selling, general and administrative expenses related to our collaboration agreements.

Product Alliances

Regeneron Collaboration

On April 8, 2019, we entered into a global, strategic collaboration with Regeneron Pharmaceuticals, Inc., or Regeneron, to discover, develop and commercialize RNAi therapeutics for a broad range of diseases by addressing therapeutic targets expressed in the eye and central nervous system, or CNS, in addition to a select number of targets expressed in the liver, which we refer to as the Regeneron Collaboration. The Regeneron Collaboration is governed by a Master Agreement, referred to as the Regeneron Master Agreement, which became effective on May 21, 2019, or the Effective Date. Upon closing of the Stock Purchase Agreement dated April 8, 2019, referred to as the Regeneron SPA, we issued 4,444,445 shares of common stock to Regeneron for aggregate cash consideration of $400.0 million, or $90.00 per share. Please read Note 10 for a full discussion regarding the Regeneron SPA. In connection with the Regeneron Master Agreement, we and Regeneron entered into (i) a binding co-co collaboration term sheet covering the continued development of cemdisiran, our C5 small interfering RNA, or siRNA, currently in Phase 2 development for C5 complement-mediated diseases, as a monotherapy and (ii) a binding license term sheet to evaluate anti-C5 antibody-siRNA combinations for C5 complement-mediated diseases including evaluating the combination of Regeneron's pozelimab (REGN3918), currently in Phase 1 development, and cemdisiran. The C5 co-co collaboration and license agreements were executed in August 2019.

Under the terms of the Regeneron Collaboration, we are working exclusively with Regeneron to discover RNAi therapeutics for eye and CNS diseases for an initial five-year research period, which we refer to as the Initial Research Term. Regeneron has an option to extend the Initial Research Term (referred to as the Research Term Extension Period, and together with the Initial Research Term, the Research Term) for up to an additional two years, for a research term extension fee of up to $400.0 million. The Regeneron Collaboration also covers a select number of RNAi therapeutic programs designed to target genes expressed in the liver, including our previously-announced collaboration with Regeneron to identify RNAi therapeutics for the chronic liver disease nonalcoholic steatohepatitis. We retain broad global rights to all of our other unpartnered liver-directed clinical and pre-clinical pipeline programs. The Regeneron Collaboration is governed by a joint steering committee that is comprised of an equal number of representatives from each party.

Regeneron will lead development and commercialization for all programs targeting eye diseases (subject to limited exceptions), entitling us to certain potential milestone and royalty payments pursuant to the terms of a license agreement, the form of which has been agreed upon by the parties. We and Regeneron will alternate leadership on CNS and liver programs, with the lead party retaining global development and commercial responsibility. For CNS and liver programs, both we and Regeneron will have the option at lead candidate selection to enter into a co-co collaboration agreement, the form of which has been agreed upon by the parties, whereby both companies will share equally all costs of, and profits from, all development and commercialization activities under the program. If the non-lead party elects to not enter into a co-co collaboration agreement with respect to a given CNS or liver program, we and Regeneron will enter into a license agreement with respect to such program and the lead party will be the "Licensee" for the purposes of the license agreement. If the lead party for a CNS or liver program elects to not enter into the co-co collaboration agreement, then we and Regeneron will enter into a license agreement with respect to such program and leadership of the program will transfer to the other party and the former non-lead party will be the "Licensee" for the purposes of the license agreement.

With respect to the programs directed to C5 complement-mediated diseases, we retain control of cemdisiran monotherapy development, and Regeneron is leading combination product development. Under the C5 co-co collaboration agreement, we and Regeneron equally share costs and potential future profits on any monotherapy program. Under the C5 license agreement, for cemdisiran to be used as part of a combination product, Regeneron is solely responsible for all development and commercialization costs and we will receive low double-digit royalties and commercial milestones of up to $325.0 million on any potential combination product sales. The C5 co-co collaboration agreement, the C5 license agreement, and the Master Agreement have been combined for accounting purposes and treated as a single agreement.

In connection with the Regeneron Master Agreement, Regeneron made an upfront payment of $400.0 million. We are also eligible to receive up to an additional $200.0 million in milestone payments upon achievement of certain criteria during early clinical development for eye and CNS programs. We and Regeneron plan to advance programs directed to up to 30 targets under the Regeneron Collaboration during the Initial Research Term. For each program, Regeneron will provide us with $2.5 million in funding at program initiation and an additional $2.5 million at lead candidate identification, with the potential for approximately $30.0 million in annual discovery funding to us as the Regeneron Collaboration reaches steady state.

Regeneron has the right to terminate the Regeneron Master Agreement for convenience upon ninety days' notice. The termination of the Regeneron Master Agreement does not affect the term of any license agreement or co-co collaboration agreement then in effect. In addition, either party may terminate the Regeneron Master Agreement for a material breach by, or insolvency of, the other party. Unless earlier terminated pursuant to its terms, the Regeneron Master Agreement will remain in effect with respect to each program until (a) such program becomes a terminated program or (b) the parties enter into a license agreement or co-co collaboration agreement with respect to such program. The Regeneron Master Agreement includes various representations, warranties, covenants, dispute escalation and resolution mechanisms, indemnities and other provisions customary for transactions of this nature.

For any license agreement subsequently entered into, the licensee will generally be responsible for its own costs and expenses incurred in connection with the development and commercialization of the collaboration products. The licensee will pay to the licensor certain development and/or commercialization milestone payments totaling up to $150.0 million for each collaboration product. In addition, following the first commercial sale of the applicable collaboration product under a license agreement, the licensee is required to make certain tiered royalty payments, ranging from low double-digits up to 20%, to the licensor based on the aggregate annual net sales of the collaboration product, subject to customary reductions.

For any co-co collaboration agreement subsequently entered into, we and Regeneron will share equally all costs of, and profits from, development and commercialization activities. In the event that a party exercises its opt-out right, the lead party will be responsible for all costs and expenses incurred in connection with the development and commercialization of the collaboration products under the applicable co-co collaboration agreement, subject to continued sharing of costs through defined points. If a party exercises its opt-out right, following the first commercial sale of the applicable collaboration product under a co-co collaboration agreement, the lead party is required to make certain tiered royalty payments, ranging from low double-digits up to 20%, to the other party based on the aggregate annual net sales of the collaboration product and the timing of the exercise of the opt-out right, subject to customary reductions and a reduction for opt-out transition costs.

Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any milestone or royalty payments from Regeneron under the Regeneron Master Agreement, the C5 license agreement, or any future license agreement, or under any co-co collaboration agreement in the event we exercise our opt-out right.

Our obligations under the Regeneron Collaboration include: (i) a research license and research services, collectively referred to as the Research Services Obligation; (ii) a worldwide license to cemdisiran for combination therapies, and manufacturing and supply and development service obligations, collectively referred to as the C5 License Obligation; and (iii) development, manufacturing and commercialization activities for cemdisiran monotherapies, referred to as the C5 Co-Co Obligation.

The research license is not distinct from the research services primarily as a result of Regeneron being unable to benefit on its own or with other resources reasonably available, as the license is providing access to specialized expertise, particularly as it relates to RNAi technology that is not available in the marketplace. Similarly, the worldwide license to cemdisiran for combination therapies is not distinct from the manufacturing and supply and development service obligations, as Regeneron cannot benefit on its own from the value of the license without receipt of supply.

Separately, the cemdisiran monotherapy co-co collaboration agreement is under the scope of ASC 808 as we and Regeneron are both active participants in the development and manufacturing activities and are exposed to significant risks and rewards that are dependent on commercial success of the activities of the arrangement. The development and manufacturing activities are a combined unit of account under the scope of ASC 808 and are not deliverables under ASC 606.

The total transaction price is comprised of the $400.0 million upfront payment and additional variable consideration related to research, development, manufacturing and supply activities related to the Research Services Obligation and the C5 License Obligation. We utilized the expected value method to determine the amount of reimbursement for these activities. We determined that any variable consideration related to sales-based royalties and milestones related to the worldwide license to cemdisiran for combination therapies is deemed to be constrained and therefore has been excluded from the transaction price. In addition, we are eligible to receive future milestones upon the achievement of certain criteria during early clinical development for the eye and CNS programs. We are also eligible to receive royalties on future commercial sales for certain eye, CNS or liver targets, if any; however, these amounts are excluded from variable consideration under the Regeneron Collaboration as we are only eligible to receive such amounts if, after a drug candidate is identified, the form of license agreement is subsequently executed resulting in a license that is granted to Regeneron. Any such subsequently granted license would represent a separate transaction under ASC 606.

We allocated the initial transaction price to each unit of account based on the applicable accounting guidance as follows, in thousands:

Performance Obligations	Standalone Selling Price	Transaction Price Allocated	Accounting Guidance
Research Services Obligation	$ 130,700	$ 183,100	ASC 606
C5 License Obligation	97,600	92,500	ASC 606
C5 Co-Co Obligation	364,600	246,000	ASC 808
		$ 521,600	

The transaction price was allocated to the obligations based on the relative estimated standalone selling prices of each obligation, over which management has applied significant judgment. We developed the estimated standalone selling price for the licenses included in the Research Services Obligation and the C5 License Obligation primarily based on the probability-weighted present value of expected future cash flows associated with each license related to each specific program. In developing such estimate, we applied judgment in the determination of the forecasted revenues, taking into consideration the applicable market conditions and relevant entity-specific factors, the expected number of targets or indications expected to be pursued under each license, the probability of success, the time needed to develop a product candidate pursuant to the associated license and the discount rate. We developed the estimated standalone selling price for the services and/or manufacturing and supply included in each of the obligations, as applicable, primarily based on the nature of the services to be performed and/or goods to be manufactured and estimates of the associated costs. The estimated standalone selling price of the C5 Co-Co Obligation was developed by estimating the present value of expected future cash flows that Regeneron is entitled to receive. In developing such estimate, we applied judgment in determining the indications that will be pursued, the forecasted revenues for such indications, the probability of success and the discount rate.

For the Research Services Obligation and the C5 License Obligation accounted for under ASC 606, we measure proportional performance over time using an input method based on cost incurred relative to the total estimated costs for each of the identified obligations, on a quarterly basis, by determining the proportion of effort incurred as a percentage of total effort we expect to expend. This ratio is applied to the transaction price allocated to each obligation. Management has applied significant judgment in the process of developing our estimates. Any changes to these estimates will be recognized in the period in which they change as a cumulative catch up. We re-evaluate the transaction price as of the end of each reporting period and during the period from the execution of the Regeneron Master Agreement through December 31, 2019, the transaction price increased $33.5 million from $521.6 million upon execution of the Regeneron Master Agreement to $555.1 million as of December 31, 2019, resulting from additional variable consideration we expect to receive. For the C5 Co-Co Obligation accounted for under ASC 808, the transaction price allocated to this obligation is recognized using a proportional performance method. Revenue recognized under this agreement, inclusive of the amount allocated to the C5 Co-Co Obligation and future cost reimbursements, is accounted for as collaboration revenue.

The following table provides a summary of the transaction price allocated to each unit of account based on the applicable accounting guidance, in addition to revenue activity during the period, in thousands:

Performance Obligations	Transaction Price Allocated	Revenue Recognized During Year Ended December 31, 2019	Deferred Revenue As of December 31, 2019	Accounting Guidance
Research Services Obligation	$ 200,600	$ 21,000	$ 84,800	ASC 606
C5 License Obligation	108,500	—	65,800	ASC 606
C5 Co-Co Obligation	246,000	2,900	243,000	ASC 808
Total	$ 555,100	$ 23,900	$ 393,600	

As of December 31, 2019, the aggregate amount of the transaction price allocated to the remaining Research Services Obligation and C5 License Obligation that was unsatisfied was $288.1 million, which is expected to be recognized through the term of the Regeneron Collaboration as the services are performed. This amount excludes the transaction price allocated to the C5 Co-Co Obligation accounted for under ASC 808. Deferred revenue related to the Regeneron Collaboration is classified as either current or non-current in the consolidated balance sheets based on the period the revenue is expected to be recognized.

Sanofi Genzyme Collaboration

2014 Sanofi Genzyme Collaboration, as amended in January 2018 and further amended in April 2019

In January 2014, we entered into the 2014 Sanofi Genzyme collaboration. 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 an Exclusive License Agreement, referred to as the Exclusive TTR License, as well as the ALN-AT3 Global License

Terms, referred to as the AT3 License Terms, as described below. The 2014 Sanofi Genzyme collaboration and the AT3 License Terms were further amended in April 2019.

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

- Upon the effective date of the 2014 Sanofi Genzyme collaboration, Sanofi Genzyme opted into a broader regional license and collaboration for patisiran, which was originally established under the 2012 Sanofi Genzyme agreement, and a co-development/co-commercialization license for revusiran. As part of our TTR program, we are also developing vutrisiran. Sanofi Genzyme had a right to elect a co-development/co-commercialization license for vutrisiran.
- In September 2015, Sanofi Genzyme elected to opt into our fitusiran clinical development program for the treatment of hemophilia 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 U.S., Canada and Western Europe, referred to as the Alnylam Territory, pursuant to the co-development/co-commercialization license terms. Upon opt-in, we retained product rights in the Alnylam Territory, while Sanofi Genzyme obtained exclusive rights to develop and commercialize fitusiran in the rest of the world, referred to as the Sanofi Genzyme Territory, and to co-commercialize the product in the Alnylam Territory. In November 2016, Sanofi Genzyme exercised that right and elected to co-develop and co-commercialize fitusiran in the Alnylam Territory. Development costs for co-development/co-commercialization products, once Sanofi Genzyme exercised an option, were shared between Sanofi Genzyme and us, with Sanofi Genzyme responsible for 50% of the global development costs. In connection with the exercise of its co-development/co-commercialization 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 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 20% for each co-development/co-commercialization product based on annual net sales, if any, in the Sanofi Genzyme Territory for such 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.
- During 2016, Sanofi Genzyme elected not to opt into the development and commercialization of givosiran or cemdisiran 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. At such time, Sanofi Genzyme had 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.

In connection with the 2018 amendment, the Exclusive TTR License and the AT3 License Terms, 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, and further agreed that no future rights would be granted to Sanofi Genzyme for co-development and co-commercialization under the 2014 Sanofi Genzyme collaboration, as amended by the 2018 amendment. During the first quarter of 2018, Sanofi Genzyme elected not to exercise its global option for our lumasiran program.

In April 2019, we and Sanofi Genzyme further amended the 2014 Sanofi Genzyme collaboration, which we refer to as the Collaboration Amendment. Under the Collaboration Amendment, we and Sanofi Genzyme agreed to conclude the research and option phase under our collaboration agreement. In connection and simultaneously with entering into the Collaboration Amendment, we and Sanofi Genzyme also entered into the Amended and Restated ALN-AT3 Global License Terms, with respect to ALN-AT3 (fitusiran) and certain back-up products, which we refer to as the A&R AT3 License Terms. The A&R AT3 License Terms amend and restate the original AT3 License Terms to modify certain of the business terms. The material collaboration terms for fitusiran continued unchanged. Such terms are described below.

Exclusive TTR License and A&R AT3 License Terms

As noted above, the 2018 amendment, together with the Exclusive TTR License and the original AT3 License Terms, revised 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. As a result, 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 is eligible to receive (i) royalties up to 25%, 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 25% beginning as of the effective date of the Exclusive TTR License, (ii) tiered royalties of 15% to 30% 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 15% based on global annual net sales of any back-up products, in each case by us, our affiliates and our sublicensees. The Collaboration Amendment entered into in April 2019 made no changes to the terms described in clauses (i)-(iii) above, which remain in full force and effect. Except as described below, there are 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 original 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, under the A&R AT3 License Terms, we are eligible to receive tiered royalties of 15% to 30% based on global annual net sales of fitusiran and up to 15% based on global annual net sales of any back-up products controlled by Sanofi Genzyme, 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.

Under the A&R AT3 License Terms, we agreed to advance, at our cost, a selected investigational asset in an undisclosed rare genetic disease through the end of Investigational New Drug-enabling studies. Following completion of such studies, we will transition, at our cost, such asset to Sanofi Genzyme. Thereafter, Sanofi Genzyme will fund all potential future development and commercialization costs for such asset. If this asset is developed and approved, we will be eligible to receive tiered double-digit royalties on global net sales.

Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any royalty payments under the A&R AT3 License Terms.

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 oversee certain matters that may arise under the Exclusive TTR License and the A&R AT3 License Terms.

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

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 A&R 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 A&R 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 in 2018, 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 was 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 had completed a substantial portion of our development obligations and determined we had sufficient information to estimate the remaining development costs for the fitusiran program and sufficient experience to reasonably estimate our development costs, the effect of which comprises the majority of the adjustment to retained earnings as a result of initially applying the new revenue accounting guidance.

We determined that the 2018 amendment, together with the Exclusive TTR License and the original AT3 License Terms, referred to as the 2018 restructured agreement, were 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 was 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 were consistent with the new revenue standard.

As noted above, the 2018 amendment, together with the Exclusive TTR License, provided 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 revenue 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 operations and 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 original AT3 License Terms, as noted above, provided Sanofi Genzyme the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products and terminated the previous co-development and co-commercialization rights related to fitusiran under the 2014 Sanofi Genzyme collaboration. The 2018 restructured agreement provided 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 was 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 was $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 applied 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 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 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 revenue on our consolidated balance sheet related to the Sanofi Genzyme agreements, 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 had the ability to measure our performance under the prior revenue standard based on costs expected to be incurred, and therefore measured 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 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.

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 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, such agreement referred to as the 2014 Investor Agreement. Under the 2014 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 ceased to beneficially own at least 5% of our outstanding common stock, Sanofi Genzyme and its affiliates were bound by certain "standstill" provisions. The standstill provisions included agreements not to acquire more than 30% of our outstanding common stock, call stockholder meetings, nominate directors other than those approved by our board of directors, subject to certain limited exceptions, or propose or support a proposal to acquire us. Further, Sanofi Genzyme agreed to vote, and cause its affiliates to vote, all shares of our voting securities they are entitled to vote, up to a maximum of 20% of our outstanding common stock, in a manner either as recommended by our board of directors or proportionally with the votes cast by our other stockholders, except with respect to certain change of control transactions or our liquidation or dissolution.

Under the 2014 Investor Agreement, Sanofi Genzyme 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 2 years if Sanofi Genzyme's option to select additional compounds under the master agreement was 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 failed to occur. Following the expiration of this lock-up period, Sanofi Genzyme would be permitted to sell such shares of common stock subject to certain limitations, including volume and manner of sale restrictions.

Finally, under the 2014 Investor Agreement, in the event Sanofi Genzyme and its affiliates acquired at least 20% or more of our outstanding common stock, Sanofi Genzyme would be entitled to appoint one individual to our board of directors. The rights and restrictions under the 2014 Investor Agreement were subject to termination upon the occurrence of certain events.

In 2014, 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 2014 Investor Agreement, in connection with our public offering in May 2017, 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. The sales of common stock to Sanofi Genzyme was not registered as part of these public offerings, though they were consummated simultaneously with the public offering.

In April 2019, in connection with the Collaboration Amendment, we and Sanofi Genzyme also entered into an Amended and Restated Investor Agreement, referred to as the A&R Investor Agreement, which amends and restates the 2014 Investor Agreement. Pursuant to the A&R Investor Agreement, Sanofi Genzyme was released from the lock-up restrictions under the 2014 Investor Agreement, as more fully described above, and was permitted to sell shares of our common stock in transactions approved by us or in fully bought block sale transactions satisfying the conditions set forth in the A&R Investor Agreement. As

of January 17, 2019, Sanofi Genzyme owned 10,554,134 shares of our common stock and as of May 3, 2019, Sanofi Genzyme reported owning no shares of our common stock.

Under the A&R Investor Agreement, until the earlier of (i) the fifth anniversary of the expiration of the last to expire royalty term or the earlier termination of the collaboration agreement, as amended by the Collaboration Amendment, and (ii) the date after December 31, 2021 on which the beneficial ownership of Sanofi Genzyme and its affiliates no longer represents at least 5% of the outstanding shares of common stock, Sanofi Genzyme and its affiliates will be bound by certain "standstill" provisions, including an agreement not to propose or support a proposal to acquire us. Under the A&R Investor Agreement, Sanofi Genzyme no longer has registration rights or the conditional right to appoint one individual to our board of directors.

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 The Medicines Company, or 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 the New Drug Application for inclisiran in the U.S., which MDCO submitted to the FDA in December 2019. 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 under the MDCO agreement.

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 will expire in the U.S. in 2034 and elsewhere 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 due to regulatory delay. 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 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 and therefore constrained. 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 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 did 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 determined that our completion of certain clinical and regulatory development tasks was relevant and directly related to our progress in completing the combined performance obligation. As such, we measured our progress upon adoption and continued 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 excluded costs that were 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, excluding non-reimbursable costs that were not deemed to directly relate to the delivery of the development services to MDCO. At the time of adoption of the new revenue standard we had completed a substantial portion of our development obligations and determined we had 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 revenue related to

the MDCO agreement 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, and we continue to 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.

On January 6, 2020, Novartis AG completed the acquisition of MDCO.

Vir Biotechnology, Inc. Alliance

In October 2017, we and Vir Biotechnology, Inc., or Vir, entered into a collaboration and license agreement, or the Vir Agreement, for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic hepatitis B virus, or HBV, infection.

Pursuant to the Vir Agreement, we granted to Vir an exclusive license to develop, manufacture and commercialize ALN-HBV02 (VIR-2218), for all uses and purposes other than certain excluded fields, as set forth in the Vir Agreement. In addition, we granted Vir an exclusive option for up to four additional RNAi therapeutic programs for the treatment of infectious diseases. Under the terms of the Vir Agreement, for each product arising from the HBV program, including ALN-HBV02, we retained the right to opt into a profit-sharing arrangement prior to the start of a Phase 3 clinical trial. In addition, we have the right on a product-by-product basis with respect to each additional infectious disease program that Vir elects to pursue, to opt into a profit-sharing arrangement for each such product at any time during a specified period prior to the initiation of a Phase 3 clinical trial for each such product.

Pursuant to the Vir Agreement, Vir paid us an upfront fee of $10.0 million and issued to us 1,111,111 shares of its common stock. Under the Vir Agreement, we may also receive milestone payments upon the achievement of certain development, regulatory and commercial milestones, as well as royalties on the net sales of licensed products ranging from high-single-digit to sub-teen double-digit percentages. Upon the achievement of a certain development milestone, we will also receive shares of Vir's common stock equal to the lesser of (i) 1,111,111 shares or (ii) a certain number of shares based on Vir's stock price at the time such milestone is achieved. As of December 31, 2019, such milestone had not yet been achieved. 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 under the Vir Agreement.

Unless terminated earlier in accordance with the terms of the agreement, the Vir Agreement expires on a licensed product-by-product and country-by-country basis upon expiration of all royalty payment obligations under the agreement. If Vir does not exercise its option for an infectious disease program, the Vir Agreement will expire upon the expiration of the applicable option period with respect to such program. However, if we exercise our profit-sharing option for any product, the term of the agreement will continue until the expiration of the profit-sharing arrangement for such product.

Either party may terminate the agreement in the event the other party fails to cure a material breach, or upon patent-related challenges by the other party. In addition, Vir has the right to terminate the agreement on a program-by-program basis or in its entirety for any reason on 90 days' written notice.

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, or the 2015 Ionis Agreement. 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. During the year ended December 31, 2019, as a result of certain payments received by us in connection with our partnered programs, we paid Ionis $21.9 million in license fees, recognized in research and development expense on our consolidated statement of operations and comprehensive loss. Similar payments to Ionis during the years ended December 31, 2018 and 2017 were not material.

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 under the Ionis agreement.

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. OTHER BALANCE SHEET DETAILS

The following table presents our inventory as of December 31, 2019 and 2018, in thousands:

	As of December 31,	
	2019	2018
Raw materials	$ 15,418	$ 8,709
Work in process	38,275	15,262
Finished goods	2,655	97
Total inventory	$ 56,348	$ 24,068

Property, plant and equipment, net consist of the following as of December 31, 2019 and 2018, in thousands:

	As of December 31,	
	2019	2018
Buildings	$ 250,380	$ —
Leasehold improvements	132,632	65,928
Construction in progress	54,195	260,975
Laboratory equipment	29,755	43,427
Computer equipment and software	14,956	13,495
Furniture and fixtures	10,339	7,238
Land	9,080	9,080
	501,337	400,143
Less: accumulated depreciation	(76,158)	(79,485)
Total	$ 425,179	$ 320,658

Accrued expenses consist of the following as of December 31, 2019 and 2018, in thousands:

	As of December 31,	
	2019	2018
Compensation and related	$ 68,304	$ 37,301
Pre-clinical, clinical trial and manufacturing	34,269	32,205
Product revenue allowances	32,670	2,696
Licensing and collaboration agreements	20,622	6,433
Consulting and professional services	14,251	10,450
Other	27,085	23,634
Total	$ 197,201	$ 112,719

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 these amounts shown in the consolidated statements of cash flows, in thousands:

	As of December 31,		
	2019	2018	2017
Cash and cash equivalents	$ 547,178	$ 420,146	$ 645,361
Restricted cash included in prepaid expenses and other current assets	4	225	—
Restricted cash included in long-term other assets	2,446	2,260	1,471
Total cash, cash equivalents, and restricted cash shown in the consolidated statements of cash flows	$ 549,628	$ 422,631	$ 646,832

The following table summarizes the changes in accumulated other comprehensive (loss) income, by component, for the years ended December 31, 2019 and 2018, in thousands:

	Loss on Investment in Joint Venture	Defined Benefit Pension Plans, Net of Tax	Unrealized (Losses) Gains from Debt Securities	Foreign Currency Translation Adjustment	Total Accumulated Other Comprehensive (Loss) Income
Balance as of December 31, 2017	$ (32,792)	$ —	$ (1,641)	$ —	$ (34,433)
Other comprehensive loss before reclassifications	—	—	(411)	—	(411)
Amounts reclassified from other comprehensive income	—	—	1,631	—	1,631
Net other comprehensive income	—	—	1,220	—	1,220
Balance as of December 31, 2018	(32,792)	—	(421)	—	(33,213)
Other comprehensive (loss) income before reclassifications	—	(3,661)	22	(343)	(3,982)
Amounts reclassified from other comprehensive income	—	141	536	—	677
Net other comprehensive (loss) income	—	(3,520)	558	(343)	(3,305)
Balance as of December 31, 2019	$ (32,792)	$ (3,520)	$ 137	$ (343)	$ (36,518)

6. FAIR VALUE MEASUREMENTS

The following tables present information about our assets that are measured at fair value on a recurring basis as of December 31, 2019 and 2018, and indicate the fair value hierarchy of the valuation techniques we utilized to determine such fair value, in thousands:

Description	As of December 31, 2019	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
Commercial paper	$ 3,439	$ —	$ 3,439	$ —
U.S. treasury securities	336,693	—	336,693	—
Money market funds	119,882	119,882	—	—
Marketable debt securities:				
Certificates of deposit	4,301	—	4,301	—
Commercial paper	36,474	—	36,474	—
Corporate notes	146,040	—	146,040	—
U.S. government-sponsored enterprise securities	32,488	—	32,488	—
U.S. treasury securities	755,714	—	755,714	—
Marketable equity securities	13,967	13,967	—	—
Restricted cash (money market funds)	1,482	1,482	—	—
Total	$ 1,450,480	$ 135,331	$ 1,315,149	$ —

Description	As of December 31, 2018	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
U.S. treasury securities	$ 221,281	$ —	$ 221,281	$ —
Money market funds	102,445	102,445	—	—
Marketable debt securities:				
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	—	—
Total	$ 989,212	$ 105,128	$ 884,084	$ —

For the years ended December 31, 2019 and 2018, 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 as of 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. As of December 31, 2019, we had no outstanding long-term debt.

In October 2017, when we entered into the Vir agreement, described above, Vir was a private clinical-stage immunology company. As part of the upfront consideration, we received 5,000,000 shares of Vir common stock. On September 27, 2019, Vir implemented a 1-for-4.5 reverse split of its common stock, converting our 5,000,000 shares to 1,111,111 shares. On October 10, 2019, Vir completed its initial public offering, or IPO. As a result of the IPO, our Vir common stock is now publicly traded and subject to a 180-day lock-up period from the effective date of Vir's IPO. During the fourth quarter of 2019, we recognized a gain of $11.3 million to record the fair market value of our Vir common stock as of December 31, 2019.

7. MARKETABLE DEBT SECURITIES

The following tables summarize our marketable debt securities as of December 31, 2019 and 2018, in thousands:

	As of December 31, 2019			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Certificates of deposit	$ 4,303	$ —	$ (2)	$ 4,301
Commercial paper	39,913	—	—	39,913
Corporate notes	146,016	58	(34)	146,040
U.S. government-sponsored enterprise securities	32,487	3	(2)	32,488
U.S. treasury securities	1,092,293	185	(71)	1,092,407
Total	$ 1,315,012	$ 246	$ (109)	$ 1,315,149

	As of December 31, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair 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	546,631	1	(124)	546,508
Total	$ 884,505	$ 1	$ (422)	$ 884,084

The fair values of our marketable debt securities by classification in the consolidated balance sheets were as follows, in thousands:

	December 31, 2019	December 31, 2018
Cash and cash equivalents	$ 340,132	$ 221,281
Marketable debt securities	975,017	662,803
Total	$ 1,315,149	$ 884,084

8. LEASES

Overview of Significant Leases

We lease three facilities for office and laboratory space in Cambridge, Massachusetts that represent substantially all of our significant lease obligations. An overview of these significant leases are as follows:

675 West Kendall Street

We lease office and laboratory space located at 675 West Kendall Street, Cambridge, Massachusetts from BMR-675 West Kendall Street, LLC, or BMR, under a non-cancelable real property lease. In September 2019, we moved our corporate headquarters and research facility to this location from our 300 Third Street location. The 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 five-year terms each. Exercise of these options was not determined to be reasonably certain and thus was not included in the operating lease liability on the consolidated balance sheet as of December 31, 2019.

Under the terms of the 675 West Kendall Lease, BMR agreed to contribute a total of $56.1 million toward the cost of base building and tenant improvements. As of December 31, 2019, in connection with base building and tenant improvements to date, we received substantially all of the funds from BMR.

In connection with the 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, 2019.

300 Third Street

We lease office and laboratory space located at 300 Third Street, Cambridge, Massachusetts 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. The term of the lease expires on January 31, 2034 with options to renew for two five-year terms each. Exercise of these options was not determined to be reasonably certain and thus was not included in the operating lease liability on the consolidated balance sheet as of December 31, 2019.

101 Main Street

We lease office space on several floors at 101 Main Street, Cambridge, Massachusetts under non-cancelable real property lease agreements by and between us and RREEF America REIT II CORP. PPP, or RREEF, entered into in March 2015 and May 2015 that will expire in March 2024 and June 2021, respectively, each with an option to renew for one five-year term. Exercise of these options was not determined to be reasonably certain and thus was not included in the operating lease liability on the consolidated balance sheet as of December 31, 2019.

Other Lease Disclosures

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. The leases do not include any restrictions or covenants that had to be accounted for under the lease guidance.

Total rent expense, including operating expenses, under our real property leases was $52.4 million, $40.6 million and $18.7 million for the years ended December 31, 2019, 2018 and 2017, respectively.

The below table summarizes our costs included in operating expenses related to right of use lease assets we have entered into through December 31, 2019, in thousands:

Description	Year Ended December 31, 2019
Operating lease cost	$ 38,613
Variable lease cost	15,209
Total	$ 53,822

Short-term lease costs were not material for the year ended December 31, 2019.

Net cash paid for the amounts included in the measurement of the operating lease liability in our consolidated balance sheet and included in operating lease liability within operating activities in our consolidated statement of cash flow was $33.7 million for the year ended December 31, 2019. The weighted-average remaining lease term and weighted-average discount rate for all leases as of December 31, 2019 was 13.2 years and 8.2%, respectively.

Future lease payments for non-cancellable operating leases and a reconciliation to the carrying amount of the operating lease liability presented in the consolidated balance sheet as of December 31, 2019 were as follows, in thousands:

Year Ending December 31	
2020	$ 29,157
2021	37,597
2022	37,754
2023	36,250
2024	35,381
2025 and thereafter	356,567
Total undiscounted lease liability	532,706
Less imputed interest	(225,873)
Less impact of future leases not yet commenced	(3,010)
Total discounted lease liability	$ 303,823
Current operating lease liability	$ 27,688
Non-current operating lease liability	276,135
Total	$ 303,823

Under the prior lease guidance, minimum payments under our non-cancelable facility leases, as of December 31, 2018, were 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
Total	$ 562,015

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 any other products we may develop. In accordance with the related license or technology agreements, we are required to make certain fixed payments to the licensor or a designee of the licensor over various agreement terms. Many of these agreement terms are consistent with the remaining lives of the underlying intellectual property that we have licensed. As of December 31, 2019, our commitments over the next five years to make fixed and cancellable payments under existing license agreements were not material.

We in-license technology from a number of sources, including Ionis and Merck Sharp & Dohme Corp, or Merck. 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 sales of our approved products. 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, during the next 12 months from the filing of this annual report on Form 10-K, potential milestone payments due to third parties, could be approximately $18.4 million, including $12.8 million in regulatory and development milestones and $5.6 million in commercial milestones, in connection with our various collaborations and license agreements. These milestones generally become due and payable upon achievement. Because the achievement of these milestones was not considered probable as of December 31, 2019, such contingencies have not been recorded in our consolidated financial statements.

Credit Agreements

On April 29, 2016, we entered into a Credit Agreement, or the Credit Agreement, by and among Alnylam U.S., Inc., as the borrower, us, as a guarantor, and Wells Fargo Bank, National Association, as the lender. The Credit Agreement was entered into in connection with the planned build out of our new drug substance manufacturing facility.

The Credit Agreement provided for a $30.0 million term loan facility and was scheduled to mature on April 29, 2021. On September 27, 2019, we repaid in full the $30.0 million outstanding principal amount under the Credit Agreement and the Credit Agreement terminated in accordance with its terms upon repayment of the outstanding indebtedness. Interest on borrowings under the Credit Agreement was calculated based on LIBOR plus 0.45%, except in the event of default.

The obligations of the borrower and us under the Credit Agreement were secured by cash collateral in an amount equal to, at any given time, at least 100% of the principal amount of all term loans outstanding under such Credit Agreement at such time. As of December 31, 2018, we recorded $30.0 million of cash collateral in connection with the Credit Agreement as restricted investments on our consolidated balance sheets.

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 commercially approved products and other 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.

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 former Chief Financial Officer in the United States District Court for the Southern District of New York. 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. On May 8, 2019, the Court entered an order appointing a lead plaintiff, and on July 3, 2019, lead plaintiff filed a consolidated class action complaint, or the Complaint. In addition to the originally named defendants, the Complaint also names as defendants certain of our other executive officers, and purports to be brought on behalf of a class of persons who acquired our securities between September 20, 2017 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, 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. All defendants filed

a motion to dismiss the Complaint in its entirety on July 31, 2019. The motion to dismiss was fully briefed on September 30, 2019.

On September 12, 2019, the Chester County Employees Retirement Fund, individually and on behalf of all others similarly situated, filed a purported securities class action complaint for violation of federal securities laws against us, certain of our current and former directors and officers, and the underwriters of our November 14, 2017 public stock offering, in the Supreme Court of the State of New York, New York County. On November 7, 2019, plaintiff filed an amended complaint, or the New York Complaint. The New York Complaint is brought on behalf of an alleged class of those who purchased our securities pursuant and/or traceable to our November 14, 2017 public stock offering. The New York Complaint purports to allege claims arising under Sections 11, 12(a)(2) and 15 of the Securities Act of 1933, as amended, and generally alleges that the defendants violated the federal securities laws by, among other things, making material misstatements or omissions concerning the results of our APOLLO Phase 3 clinical trial of patisiran. The plaintiff seeks, among other things, the designation of the action as a class action, an award of unspecified compensatory damages, rescissory damages, interest, costs and expenses, including counsel fees and expert fees, and other relief as the court deems appropriate. All defendants filed a joint motion to dismiss the New York Complaint in its entirety on December 20, 2019. Plaintiff's response to that motion was filed on February 3, 2020.

We believe that the allegations contained in these complaints are without merit and intend to defend the cases vigorously. We cannot predict at this point the length of time that these actions will be ongoing or the liabilities, 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 conjugate technology. In addition to permanent injunctive relief, we were also seeking monetary damages from Dicerna.

On April 18, 2018, we and Dicerna entered into a Settlement Agreement resolving all ongoing litigation between the companies. Under the terms of the Settlement Agreement, Dicerna was required to pay us an aggregate of $25.0 million, all of which we had received as of January 2019.

Indemnifications

In connection with license agreements we may enter with companies to obtain rights to intellectual property, we may be required to indemnify such companies for certain damages arising in connection with the intellectual property rights licensed under the agreements. Under such agreements, we may be 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 licensed intellectual property. 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, including litigation. For example, under the underwriting agreement entered into in connection with our November 2017 public offering, we have an obligation to indemnify the underwriters and each person, if any, who controls the underwriters, for certain costs and expenses arising in connection with the class action complaint filed against us and such underwriters in New York state court, described above. These indemnification costs are charged to selling, general and administrative expense.

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, 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 as of December 31, 2019 or 2018.

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. As of December 31, 2019 and 2018, 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.

Regeneron Equity Placement

On April 8, 2019, we executed the Regeneron SPA with Regeneron to sell 4,444,445 shares of our common stock for aggregate cash consideration of $400.0 million, or $90.00 per share, which we refer to as the Equity Transaction.

As a condition to consummating the transactions contemplated by the Regeneron SPA, we and Regeneron entered into an Investor Agreement dated April 8, 2019, or the Investor Agreement. Under the Investor Agreement, until the expiration or termination of the Research Term under the Regeneron Master Agreement subject to extension by one year if the Research Term or Regeneron Master Agreement is terminated by Regeneron at will, or by up to two years if as of the expiration or termination of the Research Term Regeneron owns more than 19.99% of our outstanding shares, Regeneron and its affiliates will be bound by certain "standstill" provisions. The standstill provisions include agreements not to acquire more than 30% of our outstanding shares of 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, under the Investor Agreement, Regeneron agreed to vote, and cause its affiliates to vote, all shares of our voting securities Regeneron is entitled to vote in a manner as recommended by our board of directors, except with respect to certain change of control transactions, liquidation or dissolution of our company, or, after the standstill term, any contested election of directors.

Under the Investor Agreement, Regeneron agreed not to dispose of any of the purchased shares or any shares of common stock beneficially owned by it immediately after the closing of the Regeneron Master Agreement, until the earlier of (i) the four-year anniversary of the closing of the Equity Transaction and (ii) the termination of the Regeneron Collaboration, subject to limited exceptions, which we refer to as the Lock-Up Period. Following the expiration of the Lock-Up Period, if at any time Regeneron beneficially owns at least 9.9% of our outstanding shares, then until such time as Regeneron beneficially owns less than 5% of our outstanding shares, Regeneron will not dispose of any shares except (a) pursuant to a registered underwritten public offering pursuant to the Investor Agreement, (b) in a manner consistent with the volume limitations set forth in Rule 144 under the Securities Act, or (c) as otherwise approved by us.

Under the Investor Agreement, following the Lock-Up Period, Regeneron will have three demand rights to require us to conduct a registered underwritten public offering with respect to the shares of common stock beneficially owned by Regeneron immediately after the closing of the Equity Transaction. In addition, following the Lock-Up Period, subject to certain conditions, Regeneron will be entitled to participate in registered underwritten public offerings by us if other selling stockholders are included in the registration. The rights and restrictions under the Investor Agreement are subject to termination upon the occurrence of certain events.

Under the terms of the Regeneron SPA, if at the time of closing of the Equity Transaction a sufficient number of authorized shares of common stock under our Restated Certificate of Incorporation was not available, the Equity Transaction would have been settled in the form of our Series A redeemable convertible preferred stock. On April 25, 2019, following the receipt of stockholder approval at our annual meeting, a Certificate of Amendment was filed to our Restated Certificate of Incorporation to increase the number of authorized shares of common stock from 125,000,000 to 250,000,000 shares, providing for a sufficient number of authorized shares of common stock available to be issued to Regeneron pursuant to the Equity Transaction. On May 21, 2019, subsequent to the expiration of the applicable pre-merger waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, Regeneron purchased 4,444,445 shares of our common stock for aggregate cash consideration of $400.0 million.

Because we had an obligation to Regeneron as of April 8, 2019 that may have resulted in the issuance of redeemable convertible preferred stock, we were required to follow the guidance in ASC 480 and mark-to-market the obligation to potentially issue this redeemable security until April 25, 2019, when it became known that the obligation would be fulfilled in common stock. The final mark-to-market adjustment of this obligation under ASC 480 resulted in us recording a gain of $9.4 million included in other income in the consolidated statements of operations and comprehensive loss with the offsetting adjustment to equity netting against the $400.0 million proceeds that were received upon closing.

11. STOCK-BASED COMPENSATION

Stock Plans

In May 2017, our stockholders approved a second amendment and restatement of the 2009 Stock Incentive Plan, or the Amended 2009 Plan, which increased the number of shares of common stock authorized for issuance from 11,700,000 to 15,480,000. On May 10, 2018, our stockholders approved our 2018 Stock Incentive Plan, or the 2018 Plan, which provided for the issuance of up to 3,500,000 shares in addition to the shares that remained available for grant under our Amended 2009 Plan as of the date of approval of the 2018 Plan by stockholders, and any shares underlying any awards granted under the Amended 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. In 2019, we amended the 2018 Plan to increase the shares of common stock authorized for issuance thereunder by 3,290,000. The 2018 Plan, as amended, 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.

As of December 31, 2019, an aggregate of 18,887,759 shares of common stock were reserved for issuance under our stock plans, including outstanding stock options to purchase 13,069,165 shares of common stock, 749,071 outstanding restricted stock units, 4,729,971 of common stock available for additional equity awards and 339,552 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 10 years of issuance. Time-based stock options granted to employees generally vest as to 25% of the shares on the first anniversary of the grant date and 6.25% of the shares at the end of each successive three-month period thereafter until fully vested.

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, 2019, 2018, and 2017, we recorded $2.2 million, $20.8 million and $1.1 million, respectively, related to this modification.

Inducement Equity Grants

In May 2017, our compensation committee approved the grant of 125,000 non-qualified stock options and 25,000 performance-based stock options to a newly hired executive. In February 2017, our compensation committee approved the grant of 50,000 non-qualified stock options to a newly hired vice president. The non-qualified stock options vest as to 25% of the shares on the first anniversary of the respective grant date and as to 6.25% of the shares at the end of each successive three-month period thereafter until fully vested. The performance-based stock options vested 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. These awards were made as inducement grants outside of our stockholder approved stock plans in accordance with Nasdaq Listing Rule 5635(c)(4).

Stock-Based Compensation

The following table summarizes stock-based compensation expenses included in operating costs and expenses, in thousands:

	Year Ended December 31,		
	2019	2018	2017
Research and development	$ 88,930	$ 80,509	$ 51,872
Selling, general and administrative	85,911	77,243	40,947
Total	$ 174,841	$ 157,752	$ 92,819

The following table summarizes stock-based compensation expense, in thousands:

	Year Ended December 31,		
	2019	2018	2017
Stock-based compensation expense by type of award:			
Time-based stock options	$ 99,097	$ 83,403	$ 61,802
Performance-based stock options	48,207	56,419	23,260
Time-based restricted stock units	2,351	538	541
Performance-based restricted stock units	22,123	13,144	—
ESPP share issuances	3,482	2,842	2,155
Other equity programs	1,709	1,345	1,946
Non-employee stock options	1,275	1,485	3,115
Less: Stock-based compensation expense capitalized to inventory	(3,403)	(1,424)	—
Total	$ 174,841	$ 157,752	$ 92,819

The following table summarizes our unrecognized stock-based compensation expense, net of estimated forfeitures, as of December 31, 2019 by type of awards, and the weighted-average period over which that expense is expected to be recognized:

	At December 31, 2019	
	Unrecognized Expense, Net of Estimated Forfeitures	Weighted-average Recognition Period
	(in thousands)	(in years)
Type of award:		
Time-based stock options	$ 184,062	2.62
Performance-based stock options	5,997	*
Time-based restricted stock units	7,014	1.08
Performance-based restricted stock units	12,217	*
ESPP share issuances	903	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.

The following table summarizes the Black-Scholes valuation assumption inputs for stock options granted during the years indicated:

	2019	2018	2017
Risk-free interest rate	1.4 - 2.6%	2.7 - 2.9%	1.9 -2.3%
Expected dividend yield	—	—	—
Expected option life	5.6 - 7.3 years	5.7 - 7.2 years	5.7 - 7.2 years
Expected volatility	63 - 66%	64 - 67%	61 - 67%

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, 2018	9,829	$ 72.48		
Granted	3,073	83.09		
Exercised	(1,105)	43.84		
Cancelled	(919)	89.94		
Outstanding, December 31, 2019	10,878	$ 76.92	6.67	$ 428,124
Exercisable as of December 31, 2019	6,196	$ 69.44	5.21	$ 290,437
Vested or expected to vest as of December 31, 2019	10,434	$ 76.47	6.57	$ 415,443

The weighted-average fair value of stock options granted was $49.27, $66.49 and $44.76 per share for the years ended December 31, 2019, 2018 and 2017, respectively. The intrinsic value of stock options exercised was $55.4 million, $87.1 million and $111.3 million for the years ended December 31, 2019, 2018 and 2017, 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, 2018 and 2017, 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 Price	Weighted-average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding, December 31, 2018	2,744	$ 84.75		
Granted	—	—		
Exercised	(271)	56.18		
Cancelled	(282)	96.57		
Outstanding, December 31, 2019	2,191	$ 86.77	6.35	$ 65,009
Exercisable as of December 31, 2019	1,956	$ 82.89	6.17	$ 65,009

During the years ended December 31, 2019, 2018 and 2017, there were 889,896, 763,982 and 614,796 performance-based stock options that vested, respectively. The intrinsic value of performance-based stock options exercised was $11.0 million, $8.0 million and $1.8 million for the years ended December 31, 2019, 2018 and 2017, respectively. We satisfy performance-based stock option exercises with newly issued shares of our common stock.

Restricted Stock Units and Awards

The following table summarizes the activity of our restricted stock units and awards, excluding performance-based stock units:

	Number of Units (in thousands)	Weighted-average Grant Date Fair Value
Outstanding, December 31, 2018	15	$ 89.44
Granted	127	78.01
Vested	(14)	95.66
Cancelled	(1)	89.82
Outstanding, December 31, 2019	127	$ 77.23

Performance-Based Restricted Stock Units

The following table summarizes the activity of our performance-based restricted stock units granted under our equity plans:

	Number of Units (in thousands)	Weighted-average Grant Date Fair Value
Outstanding, December 31, 2018	22	$ 91.72
Granted	685	85.01
Vested	(13)	79.14
Cancelled	(71)	85.00
Outstanding, December 31, 2019	623	$ 85.36

The performance-based restricted stock units granted in 2019 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 the year ended December 31, 2019, we recognized $20.7 million in expense related to these performance awards.

In August 2018, we recorded stock-based compensation expense of $11.8 million for 124,833 performance-based restricted stock units that fully vested upon the launch of ONPATTRO. 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 and in May 2017, our stockholders approved the Amended and Restated ESPP, providing the authorization of 1,215,789 shares for issuance. 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% of the closing price of our common stock at the beginning or end of the offering period. We issued 109,590, 78,085 and 103,666 shares during the years ended December 31, 2019, 2018 and 2017, respectively, and as of December 31, 2019, we had 339,552 shares available for issuance under the Amended and Restated ESPP.

We estimate the fair value of shares to be issued under the Amended and Restated ESPP using the Black-Scholes option-pricing model on the date of grant, or first day of the offering period. The following table summarizes information pertaining to stock purchase rights granted under the employee stock purchase plan, during the years indicated:

	2019	2018	2017
Weighted-average fair value, per share	$ 25.51	$ 35.67	$ 17.10
Weighted-average stock price volatility	52 %	63 %	91 %
Expected option life	6 months	6 months	6 months
Risk-free interest rate	2.5 %	2.0 %	0.7 %

12. INCOME TAXES

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

	2019	2018	2017
Domestic	$ (597,602)	$ (573,245)	$ (378,293)
Foreign	(288,514)	(187,429)	(112,581)
Loss before income taxes	$ (886,116)	$ (760,674)	$ (490,874)

The provision for income taxes for each of the years ended December 31, 2019, 2018 and 2017 consisted of the following:

	2019	2018	2017
Current provision:			
Domestic	$ (394)	$ —	$ —
Foreign	3,232	1,611	—
Total current provision	2,838	1,611	—
Deferred benefit:			
Federal	394	(788)	—
Foreign	(2,369)	—	—
Total deferred benefit	(1,975)	(788)	—
Total provision for income taxes	$ 863	$ 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 as of December 31, 2019 and 2018 are as follows, in thousands:

	2019	2018
Deferred tax assets:		
Net operating loss carryforwards	$ 627,466	$ 506,574
Research and development and ODC credits	261,616	220,776
AMT credits	394	788
Lease liability	69,334	—
Deferred compensation	75,058	57,268
Intangible assets	66,615	62,260
Other	13,266	20,660
Total deferred tax assets	1,113,749	868,326
Deferred tax liabilities:		
Property, plant and equipment, net	(10,077)	(6,550)
Unrealized gain on marketable securities	(3,932)	(903)
Right of use assets	(50,294)	—
Deferred tax asset valuation allowance	(1,046,013)	(860,085)
Net deferred tax asset	$ 3,433	$ 788

Our effective income tax rate differs from the statutory federal income tax rate as follows for the years ended December 31, 2019, 2018 and 2017:

	2019	2018	2017
At U.S. federal statutory rate	21.0 %	21.0 %	35.0 %
State taxes, net of federal effect	3.6	2.1	3.8
Stock-based compensation	—	0.8	3.3
Tax credits	3.7	4.2	9.9
Orphan drug credit	—	—	(3.4)
Other permanent items	(0.3)	(0.3)	(1.0)
Foreign rate differential	(6.9)	(5.3)	(8.1)
Tax reform change	—	—	(46.5)
Revaluation of deferred credits due to rate change	—	(3.5)	—
Other	(0.1)	—	(0.9)
Valuation allowance	(21.0)	(19.0)	7.9
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 assets related to certain foreign subsidiaries, and alternative minimum tax credits as these have become refundable through 2021. 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 $185.9 million, $171.8 million and $112.9 million for the years ended December 31, 2019, 2018 and 2017, respectively, primarily due to additional operating losses.

During the year ended December 31, 2019, we recorded a net provision for income taxes of $0.9 million. This is comprised of $3.2 million in current foreign tax expense offset by $2.4 million in deferred tax benefit in the foreign jurisdictions.

As of December 31, 2019, we had federal and state net operating loss carryforwards of $2.4 billion and $2.1 billion, respectively, to reduce future taxable income. As of December 31, 2019, approximately $0.9 billion of our federal net operating loss carryforward can be carried forward indefinitely while the remaining federal net operating loss of $1.5 billion expires at various dates through 2037. As of December 31, 2019, we had federal and state research and development, including Orphan Drug, and state investment tax credit carryforwards of $240.3 million and $27.0 million, respectively, available to reduce future tax liabilities that expire at various dates through 2039. As of December 31, 2019, we had alternative minimum tax credits of $0.4 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 deferred tax assets related to tax credits 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, 2019. Based on this analysis, we do not believe that any of our tax attributes will expire unutilized due to Section 382 limitations.

We apply the accounting guidance in ASC 740 related to accounting for uncertainty in income taxes. Our reserves related to taxes are based on a determination of whether, and how much of, a tax benefit taken by us in our tax filings or positions is more likely than not to be realized following resolution of any potential contingencies present related to tax benefit.

The following table presents our unrecognized tax benefits activity for the years ended December 31, 2019 and 2018, in thousands:

Description	2019	2018
Unrecognized tax benefits at the beginning of the year	$ —	$ —
Gross increases - current period tax positions	305	—
Unrecognized tax benefits at the end of the year	$ 305	$ —

The uncertain tax position does not impact our effective income tax rate due to the full valuation allowance.

The tax years 2016 through 2019 remain open to examination by major taxing jurisdictions to which we are subject, which are primarily in the U.S., although carryforward attributes generated prior to 2016 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. DEFINED BENEFIT PLANS

We maintain defined benefit plans for employees in certain countries outside the U.S., including retirement benefit plans required by applicable local law. The unfunded benefit obligation corresponds to the projected benefit obligations of which the discounted net present value is calculated based on years of employment, expected salary increases and pension adjustments, offset by the fair value of the assets held by the plan. The unfunded benefit obligation was approximately $4.3 million as of December 31, 2019 and is recorded in other liabilities on the consolidated balance sheet. The unfunded benefit obligation as of December 31, 2018 and the total net periodic benefit cost for the years ended December 31, 2019, 2018 and 2017 were not material.

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.

ALNYLAM PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

	Three Months Ended			
	March 31, 2019	June 30, 2019	September 30, 2019	December 31, 2019
	(In thousands, except per share data)			
Revenues	$ 33,294	$ 44,714	$ 70,061	$ 71,681
Operating costs and expenses	222,082	280,985	286,360	369,754
Net loss	$ (181,915)	$ (219,481)	$ (208,535)	$ (276,185)
Net loss per common share — basic and diluted	$ (1.73)	$ (2.02)	$ (1.92)	$ (2.47)
Weighted-average common shares — basic and diluted	105,400	108,576	108,701	111,750

	Three Months Ended			
	March 31, 2018	June 30, 2018	September 30, 2018	December 31, 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

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

None.

ITEM 9A. CONTROLS AND PROCEDURES

Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer (principal executive officer) and executive vice president, Chief Financial Officer (principal financial officer), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2019. 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, 2019, our Chief Executive Officer and executive 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 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, 2019. 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, 2019, 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, 2019 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report. This report appears on pages 79 and 80.

Changes in Internal Control

There were no changes in our internal control over financial reporting during the quarter ended December 31, 2019 that have materially affected, or are 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 2020 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 2020 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 2020 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 2020 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:"

(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†*	Stock Purchase Agreement dated as of January 10, 2014 by and among the Registrant, Sirna Therapeutics, Inc., Merck Sharp & Dohme Corp., and solely for the purposes of certain specified provisions, Merck & Co., Inc. (filed as Exhibit 2.1 to the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2014 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)
3.1	Restated Certificate of Incorporation of the Registrant (filed as Exhibit 3.1C to the Registrant's Current Report on Form 8-K filed on April 26, 2019 (File No. 001-36407) and incorporated herein by reference)
3.2#	Amended and Restated Bylaws of the Registrant, as amended
4.1	Specimen certificate evidencing shares of common stock (filed as Exhibit 4.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.2#	Description of Capital Stock
10.1**	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)
10.2**	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)
10.3**	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)
10.4**	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)
10.5**	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)
10.6**	Amended and Restated 2004 Employee Stock Purchase Plan (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on May 2, 2019 (File No. 001-36407) for the quarterly period ended March 31, 2019 and incorporated herein by reference)

Exhibit No.	Exhibit
10.7**	2018 Stock Incentive Plan, as amended (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2019 (File No. 001-36407) for the quarterly period ended June 30, 2019 and incorporated herein by reference)
10.8**	Forms of Incentive Stock Option Agreement, Nonstatutory Stock Option Agreements, Restricted Stock Agreement and Restricted Stock Unit Award Agreement under 2018 Stock Incentive Plan, as amended (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)
10.9**	Form of Performance Stock Unit Award Agreement under 2018 Stock Incentive Plan, as amended (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2019 (File No. 001-36407) for the quarterly period ended June 30, 2019 and incorporated herein by reference)
10.10**#	Amended and Restated Annual Incentive Program
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**	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)
10.15**	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)
10.16**	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)
10.17**	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)
10.18	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)
10.19	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)
10.20	Second Amendment to Lease, dated June 26, 2009, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on August 7, 2009 (File No. 000-50743) for the quarterly period ended June 30, 2009 and incorporated herein by reference)
10.21	Third Amendment to Lease, dated May 11, 2010, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on August 5, 2010 (File No. 000-50743) for the quarterly period ended June 30, 2010 and incorporated herein by reference)
10.22	Fourth Amendment to Lease, dated November 4, 2011, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.19 to the Registrant's Annual Report on Form 10-K filed on February 13, 2012 (File No. 000-50743) for the year ended December 31, 2011 and incorporated herein by reference)
10.23	Fifth Amendment to Lease, dated March 27, 2014, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.5 to the Registrant's Amendment No. 1 to its Quarterly Report on Form 10-Q/A filed on January 9, 2015 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)

Exhibit No.	Exhibit
10.24	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)
10.25†	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)
10.26	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)
10.27	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)
10.28	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)
10.29	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)
10.30	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)
10.31	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)
10.32†	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)
10.33†	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)
10.34†	Agreement between the Registrant, Garching Innovation GmbH (now known as Max Planck Innovation GmbH), Alnylam U.S., Inc. and Alnylam Europe AG dated June 14, 2005 (filed as Exhibit 10.8 to the Registrant's Quarterly Report on Form 10-Q filed on August 11, 2005 (File No. 000-50743) for the quarterly period ended June 30, 2005 and incorporated herein by reference)
10.35	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)
10.36	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)

Exhibit No.	Exhibit
10.37	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)
10.38†	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)
10.39†	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)
10.40†	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)
10.41†	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)
10.42†	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)
10.43†	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)
10.44†	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)
10.45†	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)
10.46	Stock Purchase Agreement dated as of April 8, 2019 by and between the Registrant and Regeneron Pharmaceuticals, Inc. (filed as Exhibit 10.6 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2019 (File No. 001-36407) for the quarterly period ended June 30, 2019 and incorporated herein by reference)
10.47†	Investor Agreement dated as of April 8, 2019 by and between the Registrant and Regeneron Pharmaceuticals, Inc. (filed as Exhibit 10.7 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2019 (File No. 001-36407) for the quarterly period ended June 30, 2019 and incorporated herein by reference)
10.48†	Master Agreement dated as of April 8, 2019 by and between the Registrant and Regeneron Pharmaceuticals, Inc., including the Form of Co-Co Collaboration Agreement and Form of License Agreement included as exhibits thereto (filed as Exhibit 10.8 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2019 (File No. 001-36407) for the quarterly period ended June 30, 2019 and incorporated herein by reference)
10.49†	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
10.50#	Amendment to License and Collaboration Agreement, dated as of November 22, 2019 between the Registrant and The Medicines Company
10.51	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)
10.52†	Amended and Restated Investor Agreement dated as of April 8, 2019 by and between the Registrant and Genzyme Corporation (filed as Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2019 (File No. 001-36407) for the quarterly period ended June 30, 2019 and incorporated herein by reference)
10.53†	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 the quarterly period ended March 31, 2014 and incorporated herein by reference)
10.54†	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)
10.55†	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)
10.56†	Amendment No. 3 entered into as of April 8, 2019 to the Master Collaboration Agreement dated as of January 11, 2014, as amended by Amendment No. 1 and Amendment No. 2, including certain Regional, Global and Co-Co License Terms attached thereto, 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 August 6, 2019 (File No. 001-36407) for the quarterly period ended June 30, 2019 and incorporated herein by reference)
10.57†	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)
10.58†	Amended and Restated ALN-AT3 Global License Terms entered into as of April 8, 2019 by and between the Registrant and Genzyme Corporation (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2019 (File No. 001-36407) for the quarterly period ended June 30, 2019 and incorporated herein by reference)
10.59†	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)
10.60†	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)
10.61†	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)
10.62†	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)
21.1#	Subsidiaries of the Registrant

Exhibit No.	Exhibit
23.1#	Consent of PricewaterhouseCoopers LLP, an Independent Registered Public Accounting Firm
31.1#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)- 14(a)/15d-14(a), by Principal Executive Officer
31.2#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)- 14(a)/15d-14(a), by Principal Financial Officer
32.1#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Executive Officer
32.2#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Financial Officer
101.SCH#	Inline XBRL Taxonomy Extension Schema Document
101.CAL#	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.LAB#	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE#	Inline XBRL Taxonomy Extension Presentation Linkbase Document
101.DEF#	Inline XBRL Taxonomy Extension Definition Linkbase Document
104	Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101.)
*	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.
†	Portions of this exhibit (indicated by asterisks) have been omitted in accordance with the rules of the Securities and Exchange Commission.
#	Filed herewith.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

Incorporated by reference from the information in our Proxy Statement for our 2020 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 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 13, 2020.

ALNYLAM PHARMACEUTICALS, INC.

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

Pursuant to the requirements of the Securities Exchange Act of 1934, the Report has been signed below by the following persons on behalf of the Registrant and in the capacities indicated as of February 13, 2020.

Name	Title
/s/ John M. Maraganore, Ph.D. John M. Maraganore, Ph.D.	Director and Chief Executive Officer (Principal Executive Officer)
/s/ Jeffrey V. Poulton Jeffrey V. Poulton	Executive 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. Paul R. Schimmel, Ph.D.	Director
/s/ Amy W. Schulman Amy W. Schulman	Director
/s/ Phillip A. Sharp, Ph.D. Phillip A. Sharp, Ph.D.	Director

Exhibit 3.2

AMENDED AND RESTATED

BYLAWS

OF
ALNYLAM PHARMACEUTICALS, INC.
(formerly Alnylam Holding Co.)

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ARTICLE I

STOCKHOLDERS

1.1 Place of Meetings. All meetings of stockholders shall be held at such place as may be designated from time to time by the Board of Directors, the Chairman of the Board or the Chief Executive Officer or, if not so designated, at the principal office of the corporation.

1.2 Annual Meeting. The annual meeting of stockholders for the election of directors and for the transaction of such other business as may properly be brought before the meeting shall be held on a date and at a time designated by the Board of Directors, the Chairman of the Board, the Chief Executive Officer or the President (if the President shall be a different individual than the Chief Executive Officer) (which date shall not be a legal holiday in the place where the meeting is to be held). If no annual meeting is held in accordance with the foregoing provisions, a special meeting may be held in lieu of the annual meeting, and any action taken at that special meeting shall have the same effect as if it had been taken at the annual meeting, and in such case all references in these Bylaws t o the annual meeting of the stockholders shall be deemed to refer to such special meeting.

1.3 Special Meetings. Special meetings of stockholders for any purpose or purposes may be called at any time by the Board of Directors, the Chairman of the Board, the Chief Executive Officer or the President (if the President shall be a different individual than the Chief Executive Officer), but such special meetings may not be called by any other person or persons. Business transacted at any special meeting of stockholders shall be limited to matters relating to the purpose or purposes stated in the notice of meeting.

1.4 Notice of Meetings. Except as otherwise provided by law, notice of each meeting of stockholders, whether annual or special, shall be given not less than 10 nor more than 60 days before the date of the meeting to each stockholder entitled to vote at such meeting. Without limiting the manner by which notice otherwise may be given to stockholders, any notice shall be effective if given by a form of electronic transmission consented to (in a manner consistent with the General Corporation Law of the State of Delaware) by the stockholder to whom the notice is given. The notices of all meetings shall state the place, date and time of the meeting and the means of remote communications, if any, by which stockholders and proxyholders may be deemed to be present in person and vote at such meeting. The notice of a special meeting shall state, in addition, the purpose or purposes for which the meeting is called. If notice is given by mail, such notice shall be deemed given when deposited in the United States mail, postage prepaid, directed to the stockholder at such stockholder’s address as it appears on the records of the corporation. If notice is given by electronic transmission, such notice shall be deemed given at the time specified in Section 232 of the General Corporation Law of the State of Delaware.

1.5 Voting List. The Secretary shall prepare, at least 10 days before every meeting of stockholders, a complete list of the stockholders entitled to vote at the meeting, arranged in alphabetical order, and showing the address of each stockholder and the number of shares registered in the name of each stockholder. Such list shall be open to the examination of any stockholder, for any purpose germane to the meeting, for a period of at least 10 days prior to the meeting: (i) on a reasonably accessible electronic network, provided that the information

required to gain access to such list is provided with notice of the meeting, or (ii) during ordinary business hours, at the principal place of business of the corporation. The list shall also be produced and kept at the time and place of the meeting during the whole time thereof, and may be inspected by any stockholder who is present.

1.6 Quorum. Except as otherwise provided by law, the Certificate of Incorporation or these Bylaws, the holders of a majority in voting power of the shares of the capital stock of the corporation issued and outstanding and entitled to vote at the meeting, present in person, present by means of remote communication in a manner, if any, authorized by the Board of Directors in its sole discretion, or represented by proxy, shall constitute a quorum for the transaction of business. A quorum, once established at a meeting, shall not be broken by the withdrawal of enough votes to leave less than a quorum.

1.7 Adjournments. Any meeting of stockholders may be adjourned from time to time to any other time and to any other place at which a meeting of stockholders may be held under these Bylaws by the stockholders present or represented at the meeting and entitled to vote, although less than a quorum, or, if no stockholder is present, by any officer entitled to preside at or to act as secretary of such meeting. It shall not be necessary to notify any stockholder of any adjournment of less than 30 days if the time and place of the adjourned meeting, and the means of remote communication, if any, by which stockholders and proxyholders may be deemed to be present in person and vote at such adjourned meeting, are announced at the meeting at which adjournment is taken, unless after the adjournment a new record date is fixed for the adjourned meeting. At the adjourned meeting, the corporation may transact any business which might have been transacted at the original meeting.

1.8 Voting and Proxies. Each stockholder shall have one vote for each share of stock entitled to vote held of record by such stockholder and a proportionate vote for each fractional share so held, unless otherwise provided by law or the Certificate of Incorporation. Each stockholder of record entitled to vote at a meeting of stockholders may vote in person (including by means of remote communications, if any, by which stockholders may be deemed to be present in person and vote at such meeting) or may authorize another person or persons to vote for such stockholder by a proxy executed or transmitted in a manner permitted by the General Corporation Law of the State of Delaware by the stockholder or such stockholder's authorized agent and delivered (including by electronic transmission) to the Secretary of the corporation. No such proxy shall be voted upon after three years from the date of its execution, unless the proxy expressly provides for a longer period.

1.9 Action at Meeting. When a quorum is present at any meeting, any matter other than the election of directors to be voted upon by the stockholders at such meeting shall be decided by the affirmative vote of the holders of a majority in voting power of the outstanding shares of stock present or represented and voting on such matter (or if there are two or more classes of stock entitled to vote as separate classes, then in the case of each such class, the holders of a majority of the stock of that class present or represented and voting on such matter), except when a different vote is required by law, applicable rule, regulation or listing agreement, the Certificate of Incorporation or these Bylaws. When a quorum is present at any meeting, any election by stockholders of directors shall be determined by a plurality of the votes cast by the stockholders entitled to vote on the election.

1.10 Nomination of Directors.

(a) Except for (i) any directors entitled to be elected by the holders of preferred stock, (ii) any directors elected in accordance with Section 2.8 hereof by the Board of Directors to fill a vacancy or newly created directorships, or (iii) as otherwise required by applicable law or stock market regulation, only persons who are nominated in accordance with the procedures in this Section 1.10 shall be eligible for election as directors. Nomination for election to the Board of Directors of the corporation at a meeting of stockholders may be made (i) by or at the direction of the Board of Directors or (ii) by any stockholder of the corporation who (x) complies with the notice procedures set forth in Section 1.10(b) and (y) is a stockholder of record on the date of the giving of such notice and on the record date for the determination of stockholders entitled to vote at such meeting.

(b) To be timely, a stockholder's notice must be received in writing by the Secretary at the principal executive offices of the corporation as follows: (x) in the case of an election of directors at an annual meeting of stockholders, not less than 90 days nor more than 120 days prior to the first anniversary of the preceding year's annual meeting; *provided, however*, that in the event that the date of the annual meeting is advanced by more than 20 days, or delayed by more than 60 days, from the first anniversary of the preceding year's annual meeting, a stockholder's notice must be so received not earlier than the 120th day prior to such annual meeting and not later than the close of business on the later of (A) the 90th day prior to such annual meeting and (B) the tenth day following the day on which notice of the date of such annual meeting was mailed or public disclosure of the date of such annual meeting was made, whichever first occurs; or (y) in the case of an election of directors at a special meeting of stockholders, provided that the Board of Directors has determined that directors shall be elected as such meeting, not earlier than the 120th day prior to such special meeting and not later than the close of business on the later of (i) the 90th day prior to such special meeting and (ii) the tenth day following the day on which notice of the date of such special meeting was mailed or public disclosure of the date of such special meeting was made, whichever first occurs. In no event shall the adjournment or postponement of an annual or special meeting (or the public announcement thereof) commence a new time (or extend any time period) for the giving of a stockholder's notice.

The stockholder's notice to the Secretary shall set forth: (a) as to each proposed nominee (i) such person's name, age, business address and, if known, residence address, (ii) such person's principal occupation or employment, (iii) the class and number of shares of stock of the corporation which are beneficially owned by such person, and (iv) any other information concerning such person that must be disclosed as to nominees in proxy solicitations pursuant to Regulation 14A under the Securities Exchange Act of 1934, as amended (the "Exchange Act"); (b) as to the stockholder giving the notice (i) such stockholder's name and address, as they appear on the corporation's books, (ii) the class and number of shares of stock of the corporation which are owned, beneficially and of record, by such stockholder, (iii) a description of all arrangements or understandings between such stockholder and each proposed nominee and any other person or persons (including their names) pursuant to which the nomination(s) are to be made by such stockholder, (iv) a representation that such stockholder intends to appear in person or by proxy at the meeting to nominate the person(s) named in its notice and (v) a representation whether the stockholder intends or is part of a group which intends (a) to deliver a proxy statement and/or form of proxy to holders of at least the percentage of the corporation's

outstanding capital stock required to elect the nominee and/or (b) otherwise to solicit proxies from stockholders in support of such nomination; and (c) as to the beneficial owner, if any, on whose behalf the nomination is being made (i) such beneficial owner's name and address, (ii) the class and number of shares of stock of the corporation which are beneficially owned by such beneficial owner, (iii) a description of all arrangements or understandings between such beneficial owner and each proposed nominee and any other person or persons (including their names) pursuant to which the nomination(s) are to be made and (iv) a representation whether the beneficial owner intends or is part of a group which intends (a) to deliver a proxy statement and/or form of proxy to holders of at least the percentage of the corporation's outstanding capital stock requirement to elect the nominee and/or (b) otherwise to solicit proxies from stockholders in support of such nomination. In addition, to be effective, the stockholder's notice must be accompanied by the written consent of the proposed nominee to serve as a director if elected. The corporation may require any proposed nominee to furnish such other information as may reasonably be required to determine the eligibility of such proposed nominee to serve as a director of the corporation. A stockholder shall not have complied with this Section 1.10(b) if the stockholder or beneficial owner, if any, on whose behalf the nomination is made solicited (or is part of a group which solicited) or did not so solicit, as the case may be, proxies in support of such stockholder's nominee in compliance with the representations with respect thereto required by this Section 1.10.

(c) The chairman of any meeting shall, if the facts warrant, have the power and duty to determine that a nomination was not made in accordance with the provisions of this Section 1.10 (including whether the stockholder or beneficial owner, if any, on whose behalf the nomination is made solicited (or is part of a group which solicited) or did not so solicit, as the case may be, proxies in support of such stockholder's nominee in compliance with the representations with respect thereto required by this Section 1.10), and if the chairman should so determine, the chairman shall so declare to the meeting and such nomination shall be disregarded.

(d) Except as otherwise required by law, nothing in this Section 1.10 shall obligate the corporation or the Board of Directors to include in any proxy statement or other stockholder communication distributed on behalf of the corporation or the Board of Directors information with respect to any nominee for director submitted by a stockholder.

(e) Notwithstanding the foregoing provisions of this Section 1.10, if the stockholder (or a qualified representative of the stockholder) does not appear at the annual or special meeting of stockholders of the corporation to present a nomination, such nomination shall be disregarded, notwithstanding that proxies in respect of such vote may have been received by the corporation. For purposes of this Section 1.10, to be considered a qualified representative of the stockholder, a person must be authorized by a writing executed by such stockholder or an electronic transmission delivered by such stockholder to act for such stockholder as proxy at the meeting of stockholders and such person must produce such writing or electronic transmission, or a reliable reproduction of the writing or electronic transmission, at the meeting of stockholders.

(f) For purposes of this Section 1.10, "public disclosure" shall include disclosure in a press release reported by the Dow Jones New Service, Associated Press or comparable national news service or in a document publicly filed by the Corporation with the Securities and Exchange Commission pursuant to Section 13, 14 or 15(d) of the Exchange Act.

1.11 Notice of Business at Annual Meetings.

(a) At any annual meeting of the stockholders, only such business shall be conducted as shall have been properly brought before the meeting. To be properly brought before an annual meeting, business must be (i) specified in the notice of meeting (or any supplement thereto) given by or at the direction of the Board of Directors, (ii) otherwise properly brought before the meeting by or at the direction of the Board of Directors, or (iii) properly brought before the meeting by a stockholder. For business to be properly brought before an annual meeting by a stockholder, (i) if such business relates to the nomination of a person for election as a director of the corporation, the procedures in Section 1.10 must be complied with and (ii) if such business relates to any other matter, the business must constitute a proper matter for stockholder action and the stockholder must (x) have given timely notice thereof in writing to the Secretary in accordance with the procedures set forth in Section 1.11(b) and (y) be a stockholder of record on the date of the giving of such notice and on the record date for the determination of stockholders entitled to vote at such annual meeting.

(b) To be timely, a stockholder's notice must be received in writing by the Secretary at the principal executive offices of the corporation not less than 90 days nor more than 120 days prior to the first anniversary of the preceding year's annual meeting; provided, however, that in the event that the date of the annual meeting is advanced by more than 20 days, or delayed by more than 60 days, from the first anniversary of the preceding year's annual meeting, a stockholder's notice must be so received not earlier than the 120th day prior to such annual meeting and not later than the close of business on the later of (A) the 90th day prior to such annual meeting and (B) the tenth day following the day on which notice of the date of such annual meeting was mailed or public disclosure of the date of such annual meeting was made, whichever first occurs. In no event shall the adjournment or postponement of an annual meeting (or the public announcement thereof) commence a new time (or extend any time period) for the giving of a stockholder's notice.

The stockholder's notice to the Secretary shall set forth as to each matter the stockholder proposes to bring before the annual meeting (i) a brief description of the business desired to be brought before the annual meeting, the text of the proposal or business (including the text of any resolutions proposed for consideration and in the event that such business includes a proposal to amend these By-laws, the language of the proposed amendment), and the reasons for conducting such business at the annual meeting, (ii) the name and address, as they appear on the corporation's books, of the stockholder proposing such business, and the name and address of the beneficial owner, if any, on whose behalf the proposal is made, (iii) the class and number of shares of stock of the corporation which are owned, of record and beneficially, by the stockholder and beneficial owner, if any, (iv) a description of all arrangements or understandings between such stockholder or such beneficial owner, if any, and any other person or persons (including their names) in connection with the proposal of such business by such stockholder and any material interest of the stockholder or such beneficial owner, if any, in such business, (v) a representation that such stockholder intends to appear in person or by proxy at the annual meeting to bring such business before the meeting and (vi) a representation whether the stockholder or the beneficial owner, if any, intends or is part of a group which intends (a) to deliver a proxy statement and/or form of proxy to holders of at least the percentage of the corporation's outstanding capital stock required to approve or adopt the proposal and/or (b) otherwise to solicit proxies from stockholders in support of such proposal. Notwithstanding

anything in these Bylaws to the contrary, no business shall be conducted at any annual meeting of stockholders except in accordance with the procedures set forth in this Section 1.11; provided that any stockholder proposal which complies with Rule 14a-8 of the proxy rules (or any successor provision) promulgated under the Securities Exchange Act of 1934, as amended, and is to be included in the corporation's proxy statement for an annual meeting of stockholders shall be deemed to comply with the requirements of this Section 1.11. A stockholder shall not have complied with this Section 1.11(b) if the stockholder or beneficial owner, if any, on whose behalf the nomination is made solicited (or is part of a group which solicited) or did not so solicit, as the case may be, proxies in support of such stockholder's nominee in compliance with the representations with respect thereto required by this Section 1.11.

(c) The chairman of any meeting shall, if the facts warrant, have the power and duty to determine that business was not properly brought before the meeting in accordance with the provisions of this Section 1.11 (including whether the stockholder or beneficial owner, if any, on whose behalf the proposal is made solicited (or is part of a group which solicited) or did not so solicit, as the case may be, proxies in support of such stockholder's proposal in compliance with the representation with respect thereto required by this Section 1.11), and if the chairman should so determine, the chairman shall so declare to the meeting and such business shall not be brought before the meeting.

(d) Notwithstanding the foregoing provisions of this Section 1.11, if the stockholder (or a qualified representative of the stockholder) does not appear at the annual meeting of stockholders of the corporation to present business, such business shall not be transacted, notwithstanding that proxies in respect of such vote may have been received by the corporation. For purposes of this Section 1.11, to be considered a qualified representative of the stockholder, a person must be authorized by a writing executed by such stockholder or an electronic transmission delivered by such stockholder to act for such stockholder as proxy at the meeting of stockholders and such person must produce such writing or electronic transmission, or a reliable reproduction of the writing or electronic transmission, at the meeting of stockholders.

(e) For purposes of this Section 1.11, "public disclosure" shall include disclosure in a press release reported by the Dow Jones New Service, Associated Press or comparable national news service or in a document publicly filed by the corporation with the Securities and Exchange Commission pursuant to Section 13, 14 or 15(d) of the Exchange Act.

1.12 Conduct of Meetings.

(a) Meetings of stockholders shall be presided over by the Chairman of the Board, if any, or in the Chairman's absence by the Vice Chairman of the Board, if any, or in the Vice Chairman's absence by the Chief Executive Officer, or in the Chief Executive Officer's absence by the President (if the President shall be a different individual than the Chief Executive Officer), or in the President's absence by a Vice President, or in the absence of all of the foregoing persons by a chairman designated by the Board of Directors, or in the absence of such designation by a chairman chosen by vote of the stockholders at the meeting. The Secretary shall act as secretary of the meeting, but in the Secretary's absence the chairman of the meeting may appoint any person to act as secretary of the meeting.

(b) The Board of Directors of the corporation may adopt by resolution such rules, regulations and procedures for the conduct of any meeting of stockholders of the corporation as it shall deem appropriate including, without limitation, such guidelines and procedures as it may deem appropriate regarding the participation by means of remote communication of stockholders and proxyholders not physically present at a meeting. Except to the extent inconsistent with such rules, regulations and procedures as adopted by the Board of Directors, the chairman of any meeting of stockholders shall have the right and authority to prescribe such rules, regulations and procedures and to do all such acts as, in the judgment of such chairman, are appropriate for the proper conduct of the meeting. Such rules, regulations or procedures, whether adopted by the Board of Directors or prescribed by the chairman of the meeting, may include, without limitation, the following: (i) the establishment of an agenda or order of business for the meeting; (ii) rules and procedures for maintaining order at the meeting and the safety of those present; (iii) limitations on attendance at or participation in the meeting to stockholders of record of the corporation, their duly authorized and constituted proxies or such other persons as shall be determined; (iv) restrictions on entry to the meeting after the time fixed for the commencement thereof; and (v) limitations on the time allotted to questions or comments by participants. Unless and to the extent determined by the Board of Directors or the chairman of the meeting, meetings of stockholders shall not be required to be held in accordance with the rules of parliamentary procedure.

(c) The chairman of the meeting shall announce at the meeting when the polls for each matter to be voted upon at the meeting will be opened and closed. If no announcement is made, the polls shall be deemed to have opened when the meeting is convened and closed upon the final adjournment of the meeting. After the polls close, no ballots, proxies or votes or any revocations or changes thereto may be accepted.

(d) In advance of any meeting of stockholders, the Board of Directors, the Chairman of the Board, the Chief Executive Officer or the President (if the President shall be a different individual than the Chief Executive Officer) shall appoint one or more inspectors or election to act at the meeting and make a written report thereof. One or more other persons may be designated as alternate inspectors to replace any inspector who fails to act. If no inspector or alternate is present, ready and willing to act at a meeting of stockholders, the chairman of the meeting shall appoint one or more inspectors to act at the meeting. Unless otherwise required by law, inspectors may be officers, employees or agents of the corporation. Each inspector, before entering upon the discharge of such inspector’s duties, shall take and sign an oath faithfully to execute the duties of inspector with strict impartiality and according to the best of such inspector’s ability. The inspector shall have the duties prescribed by law and shall take charge of the polls and, when the vote in completed, shall make a certificate of the result of the vote taken and of such other facts as may be required by law.

1.13 No Action by Consent in Lieu of a Meeting. Stockholders of the corporation may not take any action by written consent in lieu of a meeting.

ARTICLE II

DIRECTORS

2.1 General Powers. The business and affairs of the corporation shall be managed by or under the direction of a Board of Directors, who may exercise all of the powers of the corporation except as otherwise provided by law or the Certificate of Incorporation.

2.2 Number, Election and Qualification. Subject to the rights of holders of any series of Preferred Stock to elect directors, the number of directors of the Corporation shall be established by the Board of Directors. Election of Directors need not be by written ballot. Directors need not be stockholders of the corporation.

2.3 Classes of Directors. Subject to the rights of holders of any series of Preferred Stock to elect directors, the Board of Directors shall be and is divided into three classes: Class I, Class II and Class III.

2.4 Terms of Office. Subject to the rights of holders of any series of Preferred Stock to elect directors, each director shall serve for a term ending on the date of the third annual meeting following the annual meeting at which such director was elected; provided, that each director initially appointed to Class I shall serve for a term expiring at the corporation's annual meeting of stockholders held in 2005; each director initially appointed to Class II shall serve for a term expiring at the corporation's annual meeting of stockholders held in 2006; and each director initially appointed to Class III shall serve for a term expiring at the corporation's annual meeting of stockholders held in 2007; provided further, that the term of each director shall continue until the election and qualification of a successor and be subject to such director's earlier death, resignation or removal.

2.5 Quorum. The greater of (a) a majority of the directors at any time in office and (b) one-third of the number of directors fixed by the Board of Directors shall constitute a quorum for the transaction of business. If at any meeting of the Board of Directors there shall be less than such a quorum, a majority of the directors present may adjourn the meeting from time to time without further notice other than announcement at the meeting, until a quorum shall be present.

2.6 Action at Meeting. Every act or decision done or made by a majority of the directors present at a meeting duly held at which a quorum is present shall be regarded as the act of the Board of Directors unless a greater number is required by law or by the Certificate of Incorporation.

2.7 Removal. Subject to the rights of holder of any series of Preferred Stock, directors of the corporation may be removed only for cause and only by the affirmative vote of the holders of at least seventy-five percent (75%) of the votes which all the stockholders would be entitled to cast in any annual election of directors or class of directors.

2.8 Vacancies. Subject to the rights of holder of any series of Preferred Stock, any vacancy or newly created directorships on the Board of Directors, however occurring, shall be filled only by vote of a majority of the directors then in office, although less than a quorum, or by a sole remaining director and shall not be filled by the stockholders. A director elected to fill a vacancy shall hold office until the next election of the class for which such director shall have been chosen, subject to the election and qualification of a successor or until such director's earlier death, resignation or removal.

2.9 Resignation. Any director may resign by delivering a resignation in writing or by electronic transmission to the corporation at its principal office or to the Chairman of the Board, the Chief Executive Officer, the President (if the President shall be a different individual than the Chief Executive Officer) or the Secretary. Such resignation shall be effective upon receipt unless it is specified to be effective at some later time or upon the happening of some later event.

2.10 Regular Meetings. Regular meetings of the Board of Directors may be held without notice at such time and place as shall be determined from time to time by the Board of Directors; provided that any director who is absent when such a determination is made shall be given notice of the determination. A regular meeting of the Board of Directors may be held without notice immediately after and at the same place as the annual meeting of stockholders.

2.11 Special Meetings. Special meetings of the Board of Directors may be held at any time and place designated in a call by the Chairman of the Board, the Chief Executive Officer, two or more directors, or by one director in the event that there is only a single director in office.

2.12 Notice of Special Meetings. Notice of any special meeting of directors shall be given to each director by the Secretary or by the officer or one of the directors calling the meeting. Notice shall be duly given to each director (i) in person or by telephone or electronic mail at least 24 hours in advance of the meeting, (ii) by sending a telegram or telecopy or delivering written notice by hand, to such director's last known business, home or electronic mail address at least 48 hours in advance of the meeting, or (iii) by sending written notice, via first-class mail or reputable overnight courier, to such director's last known business or home address at least 72 hours in advance of the meeting. A notice or waiver of notice of a meeting of the Board of Directors need not specify the purposes of the meeting.

2.13 Meetings by Conference Communications Equipment. Directors may participate in meetings of the Board of Directors or any committee thereof by means of conference telephone or other communications equipment by means of which all persons participating in the meeting can hear each other, and participation by such means shall constitute presence in person at such meeting.

2.14 Action by Consent. Any action required or permitted to be taken at any meeting of the Board of Directors or of any committee thereof may be taken without a meeting, if all members of the Board of Directors or committee, as the case may be, consent to the action in writing or by electronic transmission, and the written consents or electronic transmissions are filed with the minutes of proceedings of the Board of Directors or committee.

2.15 Committees. The Board of Directors may designate one or more committees, each committee to consist of one or more of the directors of the corporation. The Board of Directors may designate one or more directors as alternate members of any committee, who may replace any absent or disqualified member at any meeting of the committee. In the absence or disqualification of a member of a committee, the member or members of the committee present at any meeting and not disqualified from voting, whether or not such member or members constitute a quorum, may unanimously appoint another member of the Board of Directors to act at the meeting in the place of any such absent or disqualified member. Any such committee, to the extent provided in the resolution of the Board of Directors and subject to the provisions of law, shall have and may exercise all the powers and authority of the Board of Directors in the management of the business and affairs of the corporation and may authorize the seal of the corporation to be affixed to all papers which may require it. Each such committee shall keep minutes and make such reports as the Board of Directors may from time to time request. Except as the Board of Directors may otherwise determine, any committee may make rules for the conduct of its business, but unless otherwise provided by the directors or in such rules, its business shall be conducted as nearly as possible in the same manner as is provided in these Bylaws for the Board of Directors.

2.16 Compensation of Directors. Directors may be paid such compensation for their services and such reimbursement for expenses of attendance at meetings as the Board of Directors may from time to time determine. No such payment shall preclude any director from serving the corporation or any of its parent or subsidiary entities in any other capacity and receiving compensation for such service.

ARTICLE III

OFFICERS

3.1 Titles. The officers of the corporation shall consist of a Chief Executive Officer, a President, a Secretary, a Treasurer and such other officers with such other titles as the Board of Directors may from time to time determine, including a Chairman of the Board, a Vice Chairman of the Board, a President and one or more Vice Presidents, Assistant Treasurers, and Assistant Secretaries. The Board of Directors may appoint such other officers as it may deem appropriate.

3.2 Election. The Chief Executive Officer, President, Treasurer and Secretary shall be elected annually by the Board of Directors at its first meeting following the annual meeting of stockholders. Other officers may be appointed by the Board of Directors at such meeting or at any other meeting.

3.3 Qualification. No officer need be a stockholder. Any two or more offices may be held by the same person.

3.4 Tenure. Except as otherwise provided by law, by the Certificate of Incorporation or by these Bylaws, each officer shall hold office until such officer’s successor is elected and qualified, unless a different term is specified in the resolution electing or appointing such officer, or until such officer’s earlier death, resignation or removal.

3.5 Resignation and Removal. Any officer may resign by delivering a written resignation to the corporation at its principal office or to the Chief Executive Officer or the Secretary. Such resignation shall be effective upon receipt unless it is specified to be effective at some later time or upon the happening of some later event.

Any officer may be removed at any time, with or without cause, by vote of a majority of the directors then in office.

Except as the Board of Directors may otherwise determine, no officer who resigns or is removed shall have any right to any compensation as an officer for any period following such officer's resignation or removal, or any right to damages on account of such removal, whether such officer's compensation be by the month or by the year or otherwise, unless such compensation is expressly provided in a duly authorized written agreement with the corporation.

3.6 Vacancies. The Board of Directors may fill any vacancy occurring in any office for any reason and may, in its discretion, leave unfilled for such period as it may determine any offices other than those of Chief Executive Officer, Treasurer and Secretary. Each such successor shall hold office for the unexpired term of such officer's predecessor and until a successor is elected and qualified, or until such officer's earlier death, resignation or removal.

3.7 Chairman of the Board. The Board of Directors may appoint from its members a Chairman of the Board, who need not be an employee or officer of the corporation. If the Board of Directors appoints a Chairman of the Board, such Chairman shall perform such duties and possess such powers as are assigned by the Board of Directors and, if the Chairman of the Board is also designated as the corporation's Chief Executive Officer, shall have the powers and duties of the Chief Executive Officer prescribed in Section 3.8 of these Bylaws. Unless otherwise provided by the Board of Directors, the Chairman of the Board shall preside at all meetings of the Board of Directors and stockholders.

3.8 Chief Executive Officer. The Chief Executive Officer shall have general charge and supervision of the business of the Corporation subject to the direction of the Board of Directors. The Chief Executive Officer may, but need not, also be the President.

3.9 President. If the Chief Executive Officer is not also the President, the President shall perform such duties and shall have such powers as the Board of Directors or the Chief Executive Officer may from time to time prescribe.

3.10 Vice Presidents. Any Vice President shall perform such duties and possess such powers as the Board of Directors or the Chief Executive Officer may from time to time prescribe. In the event of the absence, inability or refusal to act of the Chief Executive Officer or the President (if the President is not the Chief Executive Officer), the Vice President (or if there shall be more than one, the Vice Presidents in the order determined by the Board of Directors) shall perform the duties of the Chief Executive Officer and when so performing shall have all the powers of and be subject to all the restrictions upon the Chief Executive Officer. The Board of Directors may assign to any Vice President the title of Executive Vice President, Senior Vice President or any other title selected by the Board of Directors.

3.11 Secretary and Assistant Secretaries. The Secretary shall perform such duties and shall have such powers as the Board of Directors or the Chief Executive Officer may from time to time prescribe. In addition, the Secretary shall perform such duties and have such powers as are incident to the office of the secretary, including without limitation the duty and power to give notices of all meetings of stockholders and special meetings of the Board of Directors, to attend all meetings of stockholders and the Board of Directors and keep a record of the proceedings, to maintain a stock ledger and prepare lists of stockholders and their addresses as required, to be custodian of corporate records and the corporate seal and to affix and attest to the same on documents.

Any Assistant Secretary shall perform such duties and possess such powers as the Board of Directors, the Chief Executive Officer or the Secretary may from time to time prescribe. In the event of the absence, inability or refusal to act of the Secretary, the Assistant Secretary (or if there shall be more than one, the Assistant Secretaries in the order determined by the Board of Directors) shall perform the duties and exercise the powers of the Secretary.

In the absence of the Secretary or any Assistant Secretary at any meeting of stockholders or directors, the chairman of the meeting shall designate a temporary secretary to keep a record of the meeting.

3.12 Treasurer and Assistant Treasurers. The Treasurer shall perform such duties and shall have such powers as may from time to time be assigned by the Board of Directors or the Chief Executive Officer. In addition, the Treasurer shall perform such duties and have such powers as are incident to the office of treasurer, including without limitation the duty and power to keep and be responsible for all funds and securities of the corporation, to deposit funds of the corporation in depositories selected in accordance with these Bylaws, to disburse such funds as ordered by the Board of Directors, to make proper accounts of such funds, and to render as required by the Board of Directors statements of all such transactions and of the financial condition of the corporation.

The Assistant Treasurers shall perform such duties and possess such powers as the Board of Directors, the Chief Executive Officer or the Treasurer may from time to time prescribe. In the event of the absence, inability or refusal to act of the Treasurer, the Assistant Treasurer (or if there shall be more than one, the Assistant Treasurers in the order determined by the Board of Directors) shall perform the duties and exercise the powers of the Treasurer.

3.13 Salaries. Officers of the corporation shall be entitled to such salaries, compensation or reimbursement as shall be fixed or allowed from time to time by the Board of Directors.

ARTICLE IV

CAPITAL STOCK

4.1 Issuance of Stock. Subject to the provisions of the Certificate of Incorporation, the whole or any part of any unissued balance of the authorized capital stock of the corporation or the whole or any part of any shares of the authorized capital stock of the corporation held in the corporation’s treasury may be issued, sold, transferred or otherwise disposed of by vote of the Board of Directors in such manner, for such lawful consideration and on such terms as the Board of Directors may determine.

4.2 Certificates of Stock. Every holder of stock of the corporation shall be entitled to have a certificate, in such form as may be prescribed by law and by the Board of Directors, certifying the number and class of shares owned by such holder in the corporation. Each such certificate shall be signed by, or in the name of the corporation by, the Chairman or Vice Chairman, if any, of the Board of Directors, or the President or a Vice President, and the Treasurer or an Assistant Treasurer, or the Secretary or an Assistant Secretary of the corporation. Any or all of the signatures on the certificate may be a facsimile.

Each certificate for shares of stock which are subject to any restriction on transfer pursuant to the Certificate of Incorporation, these Bylaws, applicable securities laws or any agreement among any number of stockholders or among such holders and the corporation shall have conspicuously noted on the face or back of the certificate either the full text of the restriction or a statement of the existence of such restriction.

There shall be set forth on the face or back of each certificate representing shares of such class or series of stock of the corporation a statement that the corporation will furnish without charge to each stockholder who so requests a copy of the full text of the powers, designations, preferences and relative, participating, optional or other special rights of each class of stock or series thereof and the qualifications, limitations or restrictions of such preferences and/or rights.

4.3 Transfers. Except as otherwise established by rules and regulations adopted by the Board of Directors, and subject to applicable law, shares of stock may be transferred on the books of the corporation by the surrender to the corporation or its transfer agent of the certificate representing such shares properly endorsed or accompanied by a written assignment or power of attorney properly executed, and with such proof of authority or the authenticity of signature as the corporation or its transfer agent may reasonably require. Except as may be otherwise required by law, by the Certificate of Incorporation or by these Bylaws, the corporation shall be entitled to treat the record holder of stock as shown on its books as the owner of such stock for all purposes, including the payment of dividends and the right to vote with respect to such stock, regardless of any transfer, pledge or other disposition of such stock until the shares have been transferred on the books of the corporation in accordance with the requirements of these Bylaws.

4.4 Lost, Stolen or Destroyed Certificates. The corporation may issue a new certificate of stock in place of any previously issued certificate alleged to have been lost, stolen or destroyed, upon such terms and conditions as the Board of Directors may prescribe, including the presentation of reasonable evidence of such loss, theft or destruction and the giving of such indemnity and posting of such bond as the Board of Directors may require for the protection of the corporation or any transfer agent or registrar.

4.5 Record Date. The Board of Directors may fix in advance a date as a record date for the determination of the stockholders entitled to notice of or to vote at any meeting of stockholders, or entitled to receive payment of any dividend or other distribution or allotment of any rights in respect of any change, conversion or exchange of stock, or for the purpose of any other lawful action. Such record date shall not be more than 60 nor less than 10 days before the date of such meeting, nor more than 60 days prior to any other action to which such record date relates.

If no record date is fixed, the record date for determining stockholders entitled to notice of or to vote at a meeting of stockholders shall be at the close of business on the day before the day on

which notice is given, or, if notice is waived, at the close of business on the day before the day on which the meeting is held. If no record date is fixed, the record date for determining stockholders for any other purpose shall be at the close of business on the day on which the Board of Directors adopts the resolution relating to such purpose.

A determination of stockholders of record entitled to notice of or to vote at a meeting of stockholders shall apply to any adjournment of the meeting; provided, however, that the Board of Directors may fix a new record date for the adjourned meeting.

ARTICLE V

GENERAL PROVISIONS

5.1 Fiscal Year. Except as from time to time otherwise designated by the Board of Directors, the fiscal year of the corporation shall begin on the first day of January of each year and end on the last day of December in each year.

5.2 Corporate Seal. The corporate seal shall be in such form as shall be approved by the Board of Directors.

5.3 Waiver of Notice. Whenever notice is required to be given by law, by the Certificate of Incorporation or by these Bylaws, a written waiver signed by the person entitled to notice, or a waiver by electronic transmission by the person entitled to notice, whether before, at or after the time stated in such notice, shall be deemed equivalent to notice. Attendance of a person at a meeting shall constitute a waiver of notice of such meeting, except when the person attends a meeting for the express purpose of objecting at the beginning of the meeting, to the transaction of any business because the meeting is not lawfully called or convened.

5.4 Voting of Securities. Except as the Board of Directors may otherwise designate, the Chief Executive Officer, the President (if the President shall be a different individual than the Chief Executive Officer) or the Treasurer may waive notice of, and act as, or appoint any person or persons to act as, proxy or attorney-in-fact for this corporation (with or without power of substitution) at any meeting of stockholders or securityholders of any other entity or organization, the securities of which may be held by this corporation.

5.5 Evidence of Authority. A certificate by the Secretary, or an Assistant Secretary, or a temporary Secretary, as to any action taken by the stockholders, directors, a committee or any officer or representative of the corporation shall as to all persons who rely on the certificate in good faith be conclusive evidence of such action.

5.6 Certificate of Incorporation. All references in these Bylaws to the Certificate of Incorporation shall be deemed to refer to the Certificate of Incorporation of the corporation, as amended and in effect from time to time.

5.7 Severability. Any determination that any provision of these Bylaws is for any reason inapplicable, illegal or ineffective shall not affect or invalidate any other provision of these Bylaws.

5.8 Pronouns. All pronouns used in these Bylaws shall be deemed to refer to the masculine, feminine or neuter, singular or plural, as the identity of the person or persons may require.

ARTICLE VI

AMENDMENTS

These Bylaws may be altered, amended or repealed, in whole or in part, or new Bylaws may be adopted by the Board of Directors or by the stockholders as provided in the Certificate of Incorporation.

AMENDMENT NO. 1 TO
AMENDED AND RESTATED BYLAWS
OF
ALNYLAM PHARMACEUTICALS, INC.

Article I, Section 1.9 of the Amended and Restated Bylaws of Alnylam Pharmaceuticals, Inc. is hereby deleted in its entirety and replaced with the following:

"1.9 Action at Meeting. When a quorum is present at any meeting, any matter other than the election of directors to be voted upon by the stockholders at such meeting shall be decided by the affirmative vote of the holders of a majority in voting power of the outstanding shares of stock present or represented and voting on such matter (or if there are two or more classes of stock entitled to vote as separate classes, then in the case of each such class, the holders of a majority of the stock of that class present or represented and voting on such matter), except when a different vote is required by law, applicable rule, regulation or listing agreement, the Certificate of Incorporation or these Bylaws. When a quorum is present at any meeting, a nominee for director shall be elected to the Board of Directors if the votes cast for such nominee's election exceed the votes cast against such nominee's election; provided, however, that directors shall be elected by a plurality of votes cast at any meeting of stockholders at which there is a contested election of directors. An election shall be considered contested if as of the record date of any meeting of stockholders there are more nominees for election than positions on the Board of Directors to be filled by election at that meeting."

A new Section 5.9 is hereby added to Article V of the Amended and Restated Bylaws of Alnylam Pharmaceuticals, Inc. as follows:

"5.9 Exclusive Jurisdiction of Delaware Courts. Unless the corporation consents in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware shall be the sole and exclusive forum for any stockholder (including a beneficial owner of stock) to bring (i) any derivative action or proceeding on behalf of the corporation, (ii) any action asserting a claim of, or a claim based on, breach of a fiduciary duty owed by any current or former director, officer, employee or stockholder (including a beneficial owner of stock) of the corporation to the corporation or the corporation's stockholders (including beneficial owners of stock), (iii) any action asserting a claim against the corporation or any current or former director, officer, employee or stockholder (including a beneficial owner of stock) of the corporation arising pursuant to any provision of the General Corporation Law of the State of Delaware or the Certificate of Incorporation or Bylaws, or (iv) any action asserting a claim against the corporation or any current or former director, officer, employee or stockholder (including a beneficial owner of stock) of the corporation governed by the internal affairs doctrine."

Adopted on December 18, 2015

AMENDMENT NO. 2 TO
AMENDED AND RESTATED BYLAWS
OF
ALNYLAM PHARMACEUTICALS, INC.

Article I, Section 1 of the Amended and Restated Bylaws of Alnylam Pharmaceuticals, Inc. is hereby deleted in its entirety and replaced with the following:

"1.1 Place of Meetings. All meetings of stockholders shall be held at such place as may be designated from time to time by the Board of Directors, the Chairman of the Board or the Chief Executive Officer or, if not so designated, at the principal office of the corporation. The Board may, in its sole discretion, determine that a meeting of stockholders shall not be held at any place, but may instead be held solely by means of remote communication in the manner authorized by the General Corporation Law of the State of Delaware."

Adopted on March 8, 2018

AMENDMENT NO. 3 TO
AMENDED AND RESTATED BYLAWS
OF
ALNYLAM PHARMACEUTICALS, INC.

Article I, Section 1.3 of the Amended and Restated Bylaws of Alnylam Pharmaceuticals, Inc. is hereby deleted in its entirety and replaced with the following:

"1.3 Special Meetings.

(a) Special meetings of stockholders may be called by the Board of Directors, the Chairman of the Board or the Chief Executive Officer.

(b) A special meeting of stockholders shall be called by the Secretary at the written request or requests (each, a "Special Meeting Request" and, collectively, the "Special Meeting Requests") of holders of record who own, or are validly acting on behalf of one or more beneficial owners who own, "Net Long Shares" (as calculated in accordance with Section 1.3(f)) that represent more than fifty percent (50%) of the votes which all the stockholders of the corporation would be entitled to cast in any annual election of directors or class of directors (the "Special Meeting Requisite Percentage") and who continue to own the Special Meeting Requisite Percentage at all times between the date of the Special Meeting Request through the date of the applicable special meeting of stockholders. A beneficial owner who wishes to deliver a Special Meeting Request must cause the nominee or other person who serves as the stockholder of record of such beneficial owner's stock to sign the Special Meeting Request. If a stockholder of record is the nominee for more than one beneficial owner of stock, the stockholder of record may deliver the Special Meeting Request to call a special meeting solely with respect to the capital stock of the corporation beneficially owned by the beneficial owner who is directing the stockholder of record to sign such Special Meeting Request.

(c) A Special Meeting Request to the Secretary shall be signed and dated by each stockholder of record (whether acting for him, her or itself, or at the direction of a beneficial owner) requesting the special meeting (each, a "Requesting Stockholder"), shall comply with this Section 1.3 and Section 1.10, and shall include (i) a statement of the specific purpose or purposes of the special meeting and the exact and complete text of any proposal, (ii) the information required by the second paragraph of Section 1.10(b) and the second paragraph of Section 1.11(b) (as if such notice were submitted in connection with an annual meeting), as applicable, including any information pertaining to the stockholder which shall include such information with respect to both the beneficial owner, if any, directing such stockholder of record to sign the Special Meeting Request and to such stockholder of record (unless such stockholder of record is acting solely as a nominee for a beneficial owner) (each such beneficial owner and each stockholder of record who is not acting solely as a nominee, a "Disclosing Party"), (iii) an acknowledgement that a disposition of Net Long Shares of the corporation's capital stock owned of record or beneficially as of the date on which the Special Meeting Request in respect of such Net Long Shares is delivered to the Secretary that is made at any time prior to the special meeting shall constitute a revocation of such Special Meeting Request with respect to such disposed Net Long Shares, (iv) documentary evidence that the Disclosing Parties own the Special Meeting Requisite Percentage as of the date of such written request to the Secretary, (v) documentary evidence that the Requesting Stockholder has full power and authority to act on behalf of all beneficial owners

it purports to act for, and (vi) with respect to each business proposal to be submitted for stockholder approval at the special meeting, a statement whether or not any Disclosing Party will deliver a proxy statement and form of proxy to holders of at least the percentage of voting power of all of the shares of capital stock of the corporation required to carry such proposal (such statement, a "Solicitation Statement"). Each time the Disclosing Party's ownership position decreases following the delivery of the foregoing information to the Secretary, such Disclosing Party shall notify the corporation of his, her or its decreased ownership position, together with any information reasonably requested by the Board of Directors to verify such position, within 3 days of such decrease or as of the 5th day before the special meeting, whichever is earlier. In addition, the Requesting Stockholders and Disclosing Parties shall promptly provide any other information reasonably requested by the corporation.

(d) Notwithstanding the foregoing provisions of this Section 1.3, a special meeting requested by stockholders shall not be held if (i) the Special Meeting Request does not comply with this Section 1.3, (ii) the Special Meeting Request relates to an item of business that is not a proper subject for stockholder action under applicable law, (iii) the Special Meeting Request is received by the corporation during the period commencing one hundred twenty (120) days prior to the first anniversary of the date of the immediately preceding annual meeting and ending on the date of the next annual meeting, (iv) an annual or special meeting of stockholders that included an identical or substantially similar item of business ("Similar Business"), as determined by the Board of Directors, was held not more than one hundred twenty (120) days before the Special Meeting Request was received by the Secretary, (v) the Board of Directors has called or calls for an annual or special meeting of stockholders to be held within ninety (90) days after the Special Meeting Request is received by the Secretary and the business to be conducted at such meeting is determined by the Board of Directors to include the Similar Business, or (vi) the Special Meeting Request was made in a manner that involved a violation of Regulation 14A under the Exchange Act or other applicable law. For purposes of this Section 1.3(d), the nomination, election or removal of directors shall be deemed to be Similar Business with respect to all items of business involving the nomination, election or removal of directors, changing the size of the Board of Directors and filling of vacancies and/or newly created directorships resulting from any increase in the authorized number of directors. The Board of Directors shall determine whether the requirements set forth in this Section 1.3(d) have been satisfied.

(e) In determining whether a special meeting of stockholders has been requested by the record holders representing in the aggregate at least the Special Meeting Requisite Percentage, multiple Special Meeting Requests delivered to the Secretary will be considered together only if (i) each Special Meeting Request identifies substantially the same purpose or purposes of the special meeting and substantially the same matters proposed to be acted on at the special meeting (in each case as determined by the Board of Directors), and (ii) such Special Meeting Requests have been dated and delivered to the Secretary within sixty (60) days of the earliest dated Special Meeting Request. A Requesting Stockholder may revoke a Special Meeting Request at any time by written revocation delivered to the Secretary and if, following such revocation, there are outstanding un-revoked requests from Requesting Stockholders holding less than the Special Meeting Requisite Percentage, the Board of Directors may, in its discretion, cancel the special meeting or, if a special meeting has not yet been called, not call a special meeting. A Special Meeting Request shall be deemed to be revoked: (w) upon the first date that the aggregate ownership position of all the Disclosing Parties who are listed on the unrevoked Special Meeting

Request decreases to a number of shares of capital stock of the corporation less than the Special Meeting Requisite Percentage; (x) if any Disclosing Party does not act in accordance with the representations set forth in the Solicitation Statement delivered by such Disclosing Party or any representations made pursuant to these Bylaws; or (y) if the Requesting Stockholder or the Disclosing Party does not comply with this Section 1.3. If an actual or deemed revocation of a valid Special Meeting Request has occurred after the special meeting has been called by the Secretary, the Board of Directors shall have the discretion to determine whether or not to proceed with the special meeting.

(f) For purposes of this Section 1.3 and for determining the Special Meeting Requisite Percentage, "Net Long Shares" shall mean the number of shares beneficially owned, directly or indirectly, by any Requesting Stockholder or its affiliates that constitute such person's net long position as defined in Rule 14e-4 under the Exchange Act, (provided that for purposes of such definition the date the tender offer is first announced shall instead be the date for determining a Requesting Stockholder's Net Long Shares and the reference to the highest tender price shall refer to the market price on such date) and, to the extent not covered by such definition, reduced by any shares (i) as to which such person does not have the full economic rights (including the opportunity for profit and the risk of loss), investment rights and voting rights (including the right to vote or direct the vote at the special meeting) or (ii) as to which such person has entered into any option, warrant, forward contract, swap, contract of sale, other derivative or similar agreement, arrangement or understanding that hedges or transfers, in whole or in part, directly or indirectly, any of the economic consequences of ownership of such shares. In addition, to the extent any affiliates of the stockholder are acting in concert with the stockholder with respect to the calling of the special meeting, the determination of Net Long Shares may include the effect of aggregating the Net Long Shares (including any negative number) of such affiliate or affiliates. Whether shares constitute "Net Long Shares" shall be decided by the Board of Directors.

(g) Business transacted at all special meetings of stockholders shall be limited to the matters set forth in the corporation's notice of special meeting. Nothing contained herein shall prohibit the Board of Directors from submitting matters to the stockholders at any special meeting requested by stockholders.

(h) The chairman of any meeting shall, if the facts warrant, have the power and duty to determine that business was not properly brought before the meeting in accordance with the provisions of this Section 1.3 (including whether the stockholder solicited (or is part of a group which solicited) or did not so solicit, as the case may be, proxies in support of such stockholder's proposal in compliance with the representation with respect thereto required by this Section 1.3), and if the chairman should so determine, the chairman shall so declare to the meeting and such business shall not be brought before the meeting.

(i) Notwithstanding the foregoing provisions of this Section 1.3, if the stockholder (or a qualified representative of the stockholder) does not appear at the special meeting of stockholders of the corporation to present business, such business shall not be transacted, notwithstanding that proxies in respect of such vote may have been received by the corporation. For purposes of this Section 1.3, to be considered a qualified representative of the stockholder, a person must be authorized by a writing executed by such stockholder or an electronic transmission delivered by

such stockholder to act for such stockholder as proxy at the meeting of stockholders and such person must produce such writing or electronic transmission, or a reliable reproduction of the writing or electronic transmission, at the meeting of stockholders.

(j) Special meetings shall be held at such date and time as may be fixed by the Board of Directors in accordance with these Bylaws; *provided*, *however*, that in the case of a special meeting requested by stockholders, the date of any such special meeting shall not be more than ninety (90) days after a Special Meeting Request that satisfies the requirements of this Section 1.3 is received by the Secretary. Special meetings shall be held at such place within or without the State of Delaware as is specified in the notice of meeting."

Article I, Section 1.10(a) of the Amended and Restated Bylaws of Alnylam Pharmaceuticals, Inc. is hereby deleted in its entirety and replaced with the following:

"(a) Except for (i) any directors entitled to be elected by the holders of preferred stock, (ii) any directors elected in accordance with Section 2.8 hereof by the Board of Directors to fill a vacancy or newly created directorships, or (iii) as otherwise required by applicable law or stock market regulation, only persons who are nominated in accordance with the procedures in this Section 1.10 shall be eligible for election as directors. Nominations for election to the Board of Directors of the corporation at an annual meeting of stockholders may be made (i) by or at the direction of the Board of Directors or (ii) by any stockholder who (x) complies with the notice procedures set forth in Section 1.10(b), and (y) is a stockholder of record on the date of the giving of such notice and on the record date for the determination of stockholders entitled to vote at such meeting. Nominations for election to the Board of Directors of the corporation at a special meeting at which directors are to be elected pursuant to the corporation's notice of meeting may be made (i) by or at the direction of the Board of Directors, (ii) by stockholders pursuant to Section 1.3(c) hereof, or (iii) provided that the Board of Directors or stockholders pursuant to Section 1.3 have validly called a special meeting and directors are to be elected at such meeting, by any stockholder who (x) complies with the notice procedures set forth in Section 1.10(b), and (y) is a stockholder of record on the date of the giving of such notice and on the record date for the determination of stockholders entitled to vote at such meeting. The proposal of other business to be conducted at a special meeting of stockholders may only be made in accordance with Section 1.3."

Article I, Section 1.10(b), clause (y) of the Amended and Restated Bylaws of Alnylam Pharmaceuticals, Inc. is hereby deleted in its entirety and replaced with the following:

"…(y) in the case of a special meeting of stockholders at which directors are to be elected pursuant to the corporation's notice of meeting, not earlier than the 120th day prior to such special meeting and not later than the close of business on the later of (i) the 90th day prior to such special meeting and (ii) the tenth day following the day on which notice of the date of such special meeting was mailed or public disclosure of the date of such special meeting was made, whichever first occurs."

Adopted on March 1, 2019; Effective as of April 25, 2019

DESCRIPTION OF THE COMPANY'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

The following description of the capital stock of Alnylam Pharmaceuticals, Inc. ("us," "our," "we" or the "Company") is intended as a summary only. This description is based upon, and is qualified by reference to, our amended and restated certificate of incorporation, our amended and restated bylaws and applicable provisions of the Delaware General Corporation Law (the "DGCL"). This summary is not complete. You should read our amended and restated certificate of incorporation, previously filed with the Securities and Exchange Commission (the "SEC") and incorporated by reference as Exhibit 3.1 to this Annual Report on Form 10-K for the year ended December 31, 2019 (this "Annual Report") of which this Exhibit 4.2 is a part, and amended and restated bylaws, filed with the SEC as Exhibit 3.2 to this Annual Report. We encourage you to read our certificate of incorporation, bylaws and the applicable portions of the DGCL carefully.

Authorized Capital Stock

Our authorized capital stock consists of two hundred fifty million (250,000,000) shares of common stock, par value $0.01 per share, and five million (5,000,000) shares of preferred stock, par value $0.01 per share, all of which shares of preferred stock are undesignated.

Common Stock

Voting Rights. Each holder of the common stock is entitled to one vote for each share held on all matters to be voted upon by stockholders, except on any amendment to our certificate of incorporation that relates solely to the terms of one or more outstanding series of preferred stock if the holders of such affected series are entitled to vote thereon.

Dividends. The holders of the common stock, after any preferences of holders of any preferred stock, are entitled to receive dividends when, as and if declared by the board of directors out of legally available funds.

Liquidation and Dissolution. If we are liquidated or dissolved, the holders of the common stock will be entitled to share in our assets available for distribution to stockholders in proportion to the amount of common stock they own. The amount available for common stockholders is calculated after payment of liabilities. Holders of any preferred stock will receive a preferential share of our assets before the holders of the common stock receive any assets.

Other Rights. Holders of the common stock have no right to:

- convert the stock into any other security;
- have the stock redeemed; or
- purchase additional stock or to maintain their proportionate ownership interest.

The common stock does not have cumulative voting rights. Holders of shares of the common stock are not required to make additional capital contributions.

Our common stock is listed and traded on The NASDAQ Stock Market LLC under the symbol "ALNY."

Transfer Agent and Registrar. Computershare Trust Company, N.A. is the transfer agent and registrar for the common stock.

Preferred Stock

We may issue shares of our preferred stock from time to time, in one or more series. Our board of directors will determine the rights, preferences and privileges of the shares of each wholly unissued series, and any qualifications, limitations or restrictions thereon, including dividend rights, conversion rights, preemptive rights, terms of redemption or repurchase, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of any series. Convertible preferred stock will be convertible into our common stock or exchangeable for other securities. Conversion may be mandatory or at the holder's option and would be at prescribed conversion rates.

If we sell any series of preferred stock, we will fix the rights, preferences and privileges of the preferred stock of such series, as well as any qualifications, limitations or restrictions thereon, in the certificate of designation relating to that series.

Effects of Authorized but Unissued Stock

We have shares of common stock and preferred stock available for future issuance without stockholder approval, subject to any limitations imposed by the listing standards of The Nasdaq Global Select Market. We may utilize these additional shares for a variety of corporate purposes, including for future public offerings to raise additional capital or facilitate corporate acquisitions or for payment as a dividend on our capital stock. The existence of unissued and unreserved common stock and preferred stock may enable our board of directors to issue shares to persons friendly to current management or to issue preferred stock with terms that could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a controlling interest in our company by means of a merger, tender offer, proxy contest or otherwise. In addition, if we issue preferred stock, the issuance could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation.

Registration Rights

In April 2019, we entered into an investor agreement with Regeneron Pharmaceuticals, Inc. ("Regeneron") in connection with our global, strategic collaboration. The investor agreement provides that, following the expiration of the lock-up period described in the investor agreement, Regeneron will have will have three demand rights to require the Company to conduct a registered underwritten public offering with respect to the 4,444,445 shares of our common stock purchased by Regeneron in May 2019. In addition, following the expiration of such lock-up period and until the tenth anniversary of such expiration or the date Regeneron no longer owns at least 5 percent of our common stock, Regeneron will be entitled to register such shares in our registered underwritten public offerings if other selling stockholders are included in the registration. These registration rights are subject to conditions and limitations, including the right, in certain circumstances, of the underwriters of an offering to limit the number of shares included in such registration, our right not to effect a demand registration more than once in any twelve-month period, and minimum thresholds for the number of shares that may comprise a demand registration.

Provisions of Our Certificate of Incorporation and Bylaws and Delaware Law That May Have Anti-Takeover Effects

Board of Directors. Our certificate of incorporation and bylaws provide for a board of directors divided as nearly equally as possible into three classes. Each class is elected to a term expiring at the annual meeting of stockholders held in the third year following the year of such election. The number of directors comprising our board of directors is fixed from time to time by the board of directors.

Removal of Directors by Stockholders. Under our bylaws, members of our board of directors may only be removed for cause by the affirmative vote of the holders of at least 75 percent of the outstanding shares entitled to vote on the election of the directors.

Stockholder Nomination of Directors. Our bylaws provide that a stockholder must notify us in writing of any stockholder nomination of a director not earlier than the 120th day and not later the 90th day prior to the first anniversary of the preceding year's annual meeting; provided, that if the date of the annual meeting is advanced by more than 20 days, or delayed by more than 60 days from the first anniversary of the preceding year's annual meeting, notice must be received not earlier than the 120th day prior to such annual meeting and not later than the close of business on the later of (1) the 90th day prior to such annual meeting and (2) the 10th day following the date on which notice of the date of such annual meeting was mailed or public disclosure of the date of such annual meeting was made, whichever occurs first. Our bylaws also specify requirements relating to the content of the notice which stockholders must provide, including a stockholder nomination for election to our board of directors, to be properly presented at the annual meeting.

No Action By Written Consent. Our certificate of incorporation provides that our stockholders may not act by written consent and may only act at duly called meetings of stockholders.

Delaware Business Combination Statute. Section 203 of the DGCL is applicable to us. Section 203 of the DGCL restricts some types of transactions and business combinations between a corporation and a 15 percent stockholder. A 15 percent stockholder is generally considered by Section 203 to be a person owning 15 percent or more of the corporation's outstanding voting stock. Section 203 refers to a 15 percent stockholder as an "interested stockholder." Section 203 restricts these transactions for a period of three years from the date the stockholder acquires 15 percent or more of our outstanding voting stock. With some exceptions, unless the transaction is approved by the board of directors and the holders of at least two-thirds of our outstanding voting stock, Section 203 prohibits significant business transactions such as:

- a merger with, disposition of significant assets to or receipt of disproportionate financial benefits by the interested stockholder, and
- any other transaction that would increase the interested stockholder's proportionate ownership of any class or series of our capital stock.
- The shares held by the interested stockholder are not counted as outstanding when calculating the two-thirds of the outstanding voting stock needed for approval.
- The prohibition against these transactions does not apply if:
- prior to the time that any stockholder became an interested stockholder, the board of directors approved either the business combination or the transaction in which such stockholder acquired 15 percent or more of our outstanding voting stock, or
- the interested stockholder owns at least 85 percent of our outstanding voting stock as a result of a transaction in which such stockholder acquired 15 percent or more of our outstanding voting stock. Shares held by persons who are both directors and officers or by some types of employee stock plans are not counted as outstanding when making this calculation.

Directors' Liability

Our certificate of incorporation provides that a member of the board of directors will not be personally liable to us or our stockholders for monetary damages for breaches of their legal duties to us or our stockholders as a director, except for liability:

- for any breach of the director's legal duty to act in the best interests of us and our stockholders;

- for acts or omissions by the director with dishonest intentions or which involve intentional misconduct or an intentional violation of the law;
- for declaring dividends or authorizing the purchase or redemption of shares in violation of Delaware law; or
- for transactions where the director derived an improper personal benefit.

A Delaware corporation may “opt out” of these provisions with an express provision in its original certificate of incorporation or an express provision in its certificate of incorporation or bylaws resulting from a stockholders’ amendment approved by at least a majority of the outstanding voting shares. We have not opted out of these provisions. As a result, mergers or other takeover or change in control attempts of us may be discouraged or prevented.

Our certificate of incorporation provides that we must indemnify our directors to the fullest extent permitted by Delaware law, and we are required to advance expenses, as incurred, to our directors in connection with a legal proceeding to the fullest extent permitted by Delaware law. We have also entered into indemnification agreements with our directors, in addition to the indemnification provided for in our certificate of incorporation, and intend to enter into indemnification agreements with any new directors in the future. We have purchased and intend to maintain insurance on behalf of any person who is or was a director against any loss arising from any claim asserted against him or her and incurred by him or her in any such capacity, subject to certain exclusions.

Alnylam Pharmaceuticals, Inc. Annual Incentive Program

Purpose

The Compensation Committee of the Board of Directors (the "Board") of Alnylam Pharmaceuticals, Inc. ("Alnylam") has recommended and the Board has approved this Annual Incentive Program (the "Bonus Plan") to incent and reward eligible employees of Alnylam or any of its affiliates (subject to applicable local laws) (collectively, the "Company"), based upon their performance relative to pre-established corporate and individual goals and objectives, and to retain Company employees by establishing an important element of the Company's total rewards package consistent with the Company's compensation philosophy and operating strategy.

Eligibility

All regular employees who are not otherwise participating in any field-based incentive plan established by the Company, and who are employed by the Company both on or before October 1 of a calendar year (each, a "Plan Year") and on the date of payment of any Bonus Award (as defined herein) hereunder, (collectively, "Plan Participants"), are eligible to receive an annual cash bonus (a "Bonus Award") based upon achievement of individual and/or corporate goals and objectives for such Plan Year. The Compensation Committee may, in its discretion, include employees who join the Company or one of its affiliates after October 1 of a Plan Year as Plan Participants. Bonus Awards for Plan Participants who have been employed with the Company or one of its affiliates for less than one year as of the last day of a Plan Year may be pro-rated by the Compensation Committee, in its discretion. In addition, Bonus Awards for Plan Participants who have been on an approved leave of absence for in excess of twelve consecutive weeks during the applicable Plan Year may be pro-rated by the Compensation Committee, in its discretion (subject to applicable local laws).

Goals

The corporate goals for each Plan Year, including the percentage weighting for such goals, shall be proposed by the Company's executive officers, reviewed by the Compensation Committee and approved by the Board. Except as the Compensation Committee may otherwise determine, Bonus Awards for the Company's executive officers will be based entirely upon achievement of the corporate goals. Individual objectives for all other Plan Participants shall be approved by the employees' direct supervisor.

Awards

Under the Bonus Plan, each Plan Participant shall have an established target award, representing a percentage of the Plan Participant's annual base salary (a "Target Award"). Unless the Compensation Committee otherwise determines, the Target Award shall be based upon the Plan Participant's base salary and job level as of the last day of the applicable Plan Year.

Bonus Awards under the Bonus Plan, if any, will be determined by first establishing a bonus pool (the "Bonus Pool"). The Bonus Pool will be calculated by (1) aggregating each Plan Participant's Target Award, (2) multiplying that sum by one hundred and four percent (104%), and then (3) multiplying that

sum by a modifier established by the Board that is based on the Company's performance as measured against the applicable Plan Year's corporate goals (the "Corporate Performance Level"). The Compensation Committee shall also have the discretion to set a "minimum" threshold and/or a "maximum" amount with respect to the Corporate Performance Level.

The Bonus Pool will then be allocated among the Plan Participants based upon consideration of each Plan Participant's title/level and salary (as reflected by their Target Award percentage) and (i) with respect to Plan Participants who are executive officers, the Corporate Performance Level (except as the Compensation Committee may otherwise determine), and (ii) with respect to all other Plan Participants, their year-end performance ratings for such Plan Year, which shall be determined by their performance against their individual objectives for such Plan Year, overall job performance and support of the Company's core values.

The Compensation Committee retains the discretion under the Bonus Plan to adjust upward or downward any Bonus Award and/or the Bonus Pool as it deems appropriate.

By no later than January 31 of the year following the applicable Plan Year, the Compensation Committee, and the full Board of Directors, as applicable, plans to evaluate the Company's performance against the established corporate goals, establish the Bonus Pool, if any, available under the Bonus Plan and approve the individual Bonus Awards for each executive officer and each other employee at the level of Senior Vice President or higher. The Company's management will evaluate the individual performance and contributions of the other Plan Participants, and determine the amount of the Bonus Awards to be granted from the Bonus Pool to such other Plan Participants. This determination is expected to be made on or before February 28 of the year following the applicable Plan Year and any Bonus Awards granted to Plan Participants under the Bonus Plan shall be made in cash and paid before March 15 of the year following the applicable Plan Year.

Administration; Amendment

The Bonus Plan is administered by the Compensation Committee. The Compensation Committee has full power and authority to interpret and make all decisions regarding the Bonus Plan, and its decisions and interpretations are final and binding on all Plan Participants. The Compensation Committee or the full Board may amend the Bonus Plan in any manner at any time without the consent of any Plan Participant.

Approved by Board of Directors March 8, 2018
Amended October 7, 2019

Amendment to License and Collaboration Agreement

This AMENDMENT TO LICENSE AND COLLABORATION AGREEMENT (this "Amendment"), dated as of November 22, 2019, is entered into between Alnylam Pharmaceuticals, Inc., a corporation organized and existing under the laws of the State of Delaware ("Alnylam"), and The Medicines Company, a corporation organized and existing under the laws of Delaware ("MedCo") (each individually a "Party" and, collectively, the "Parties").

W I T N E S S E T H

WHEREAS, the Parties entered into a License and Collaboration Agreement, effective as of February 3, 2013 (the "Original Agreement"), pursuant to which the Parties agreed to collaborate in the development of certain proprietary therapeutic products targeting the human PCSK9 gene; and

WHEREAS, the Parties desire to amend the Original Agreement as set forth in this Amendment.

NOW THEREFORE, in consideration of the premises and covenants set forth herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, each of the Parties hereby agrees as follows:

Section 1.01 Amendment. Effective as of the consummation of the Change of Control of MedCo pursuant to the Agreement and Plan of Merger by and among MedCo, Novartis AG and Medusa Merger Corporation, to be entered into promptly following the date of this Amendment, as may be amended from time to time (the "**Merger Agreement**", and such time of consummation, the "**Acquisition Effective Time**"), Section 6.7 of the Original Agreement is hereby replaced in full with the following:

> 6.7 **No Reach Through to Acquirer IP**. Notwithstanding anything in this Agreement to the contrary, following the closing of a Change of Control of a Party (the "**Acquired Party**"), the Parties agree that the other Party (the "**Non-Acquired Party**") shall not obtain rights or access to the Patent Rights or Know-How controlled by the Acquirer (as defined below) or any of the Affiliates of such Acquirer (other than the Acquired Party and its Affiliates which exist immediately prior to the closing of such Change of Control (such Affiliates, the "**Pre-Existing Affiliates**")), other than with respect to, (a) when MedCo is an Acquired Party, (i) all MedCo Improvements, Joint Collaboration IP, MedCo Collaboration IP, MedCo Patent Rights, MedCo Know-How and MedCo Technology and (ii) the terms in Section 12.3, in each case ((i) and (ii)) with references to Medco and its Affiliates in those six definitions and Section 12.3 including the Acquirer and all its Affiliates (including, for clarity, MedCo and its Pre-Existing Affiliates after the closing of a Change of Control of MedCo), and (b) when Alnylam is an Acquired Party, all Alnylam Collaboration IP and Joint Collaboration IP with references to Alnylam and its Affiliates in those two definitions including the Acquirer and all of its Affiliates (including, for clarity, Alnylam and its Pre-Existing Affiliates after the closing of a

Change of Control of Alnylam); and, in each case ((a)-(b)), the Acquirer and its Affiliates (other than the Acquired Party and its Pre-Existing Affiliates) shall be bound by the restrictions set forth in Section 9.5.1 only with respect to any siRNA Product (but not any non-siRNA compound or molecule). For clarity but without limitation, the Non-Acquired Party's rights in all Patent Rights and Know-How Controlled by the Acquired Party or any of its Pre-Existing Affiliates, which Patent Rights and Know-How exist as of the date of the closing of such Change of Control and are then licensed hereunder to the Non-Acquired Party, shall remain licensed to such Non-Acquired Party after the date of the closing of such Change of Control in accordance with and subject to the terms and conditions of this Agreement and shall not be affected in any manner by virtue of such Change of Control. "Acquirer" means, with respect to the Acquired Party, the Third Party that acquires such Acquired Party or its direct or indirect controlling Affiliate, or that acquires all or substantially all of the assets of the Acquired Party or its direct or indirect controlling Affiliate.

Section 1.02 Amendment to Schedules. Effective as of the Acquisition Effective Time, Schedule C-2 of the Original Agreement is hereby amended to include U.S. Patent No. 10,125,369, U.S. Patent Application No. 15/895023, and all Patent Rights (as defined in the Original Agreement) that claim priority to or have common priority with any of the foregoing.

Section 1.03 Termination. This Amendment shall terminate and be of no further force and effect upon the termination of the Merger Agreement prior to the consummation of the Change of Control of MedCo contemplated therein.

Section 1.04 Miscellaneous. Except as expressly amended by this Amendment, the Original Agreement remains in full force and effect. This Amendment contains the entire understanding of the Parties with respect to the subject matter hereof, and supersedes all previous arrangements with respect to the subject matter hereof. This Amendment shall be construed and the respective rights of the Parties determined in accordance with the substantive laws of the State of New York, notwithstanding any provisions of New York law governing conflicts of laws to the contrary, and the patent laws of the relevant jurisdiction without reference to any rules of conflict of laws. This Amendment may be executed in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Facsimile signatures and signatures transmitted via PDF shall be treated as original signatures.

[*Signature Page Follows*]

IN WITNESS WHEREOF, the Parties hereto have caused this Amendment to be executed as of the date first written above.

Alnylam Pharmaceuticals, Inc.

By: /s/ Laurie B. Keating

Name: Laurie B. Keating
Title: EVP, Chief Legal Officer

The Medicines Company

By: /s/ Mark Timney

Name: Mark Timney
Title: CEO

EXHIBIT 21.1

SUBSIDIARIES OF THE REGISTRANT

Name	Ownership Percentage	Jurisdiction of Organization
Alnylam U.S., Inc.	100%	Delaware
Alnylam Securities Corporation	100%	Massachusetts
Sirna Therapeutics, Inc.	100%	Delaware
Alnylam Austria GmbH	100%	Austria
Alnylam Belgium BVBA	100%	Belgium
Alnylam Brasil Farmaceutica Ltda	99%	Brazil
Alnylam (Bermuda) Ltd.	100%	Bermuda
Alnylam Canada ULC	100%	Canada
Alnylam France SAS	100%	France
Alnylam Europe AG	100%	Germany
Alnylam Germany GmbH	100%	Germany
Alnylam Italy Srl	100%	Italy
Alnylam Japan KK	100%	Japan
Alnylam Netherlands BV	100%	Netherlands
Alnylam Pharmaceuticals Spain SL	100%	Spain
Alnylam Sweden AB	100%	Sweden
Alnylam Switzerland GmbH	100%	Switzerland
Alnylam Taiwan Co., Ltd.	100%	Taiwan
ALNYPT Unipessoal Lda	100%	Portugal
Alnylam UK Limited	100%	United Kingdom
Alnylam Czech s.r.o.	100%	Czech Republic

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statement on Forms S-8 (Nos. 333-190498, 333-127450, 333-116151, 333-148114, 333-157633, 333-165105, 333-172370, 333-207251, 333-219840 and 333-226533) and Form S-3 (No. 333-217688) of Alnylam Pharmaceuticals, Inc. of our report dated February 13, 2020 relating to the financial statements and the effectiveness of internal control over financial reporting, which appears in this Form 10-K.

/s/PricewaterhouseCoopers LLP
Boston, Massachusetts
February 13, 2020

Exhibit 31.1

CERTIFICATION

I, John M. Maraganore, Ph.D., certify that:

1) I have reviewed this Annual Report on Form 10-K of Alnylam Pharmaceuticals, Inc.;

2) Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3) Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4) The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, 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;

   c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5) The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 13, 2020

/s/ John M. Maraganore

John M. Maraganore, Ph.D.
Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, Jeffrey V. Poulton, certify that:

1) I have reviewed this Annual Report on Form 10-K of Alnylam Pharmaceuticals, Inc.;

2) Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3) Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4) The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, 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;

   c. Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5) The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 13, 2020

/s/ Jeffrey V. Poulton

Jeffrey V. Poulton
Executive Vice President, Chief Financial Officer

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Alnylam Pharmaceuticals, Inc. (the "Company") for the fiscal year ended December 31, 2019 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, John M. Maraganore, Ph.D., Chief Executive Officer of the Company, hereby certifies, pursuant to Section 1350 of Chapter 63 of Title 18, United States Code, that, to his knowledge:

1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 13, 2020

/s/ John M. Maraganore

John M. Maraganore, Ph.D
Chief Executive Officer

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Alnylam Pharmaceuticals, Inc. (the "Company") for the fiscal year ended December 31, 2019 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Jeffrey V. Poulton, Executive Vice President, Chief Financial Officer, hereby certifies, pursuant to Section 1350 of Chapter 63 of Title 18, United States Code, that, to his knowledge:

1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 13, 2020

/s/ Jeffrey V. Poulton

Jeffrey V. Poulton
Executive Vice President, Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.