A YEAR LIKE NO OTHER

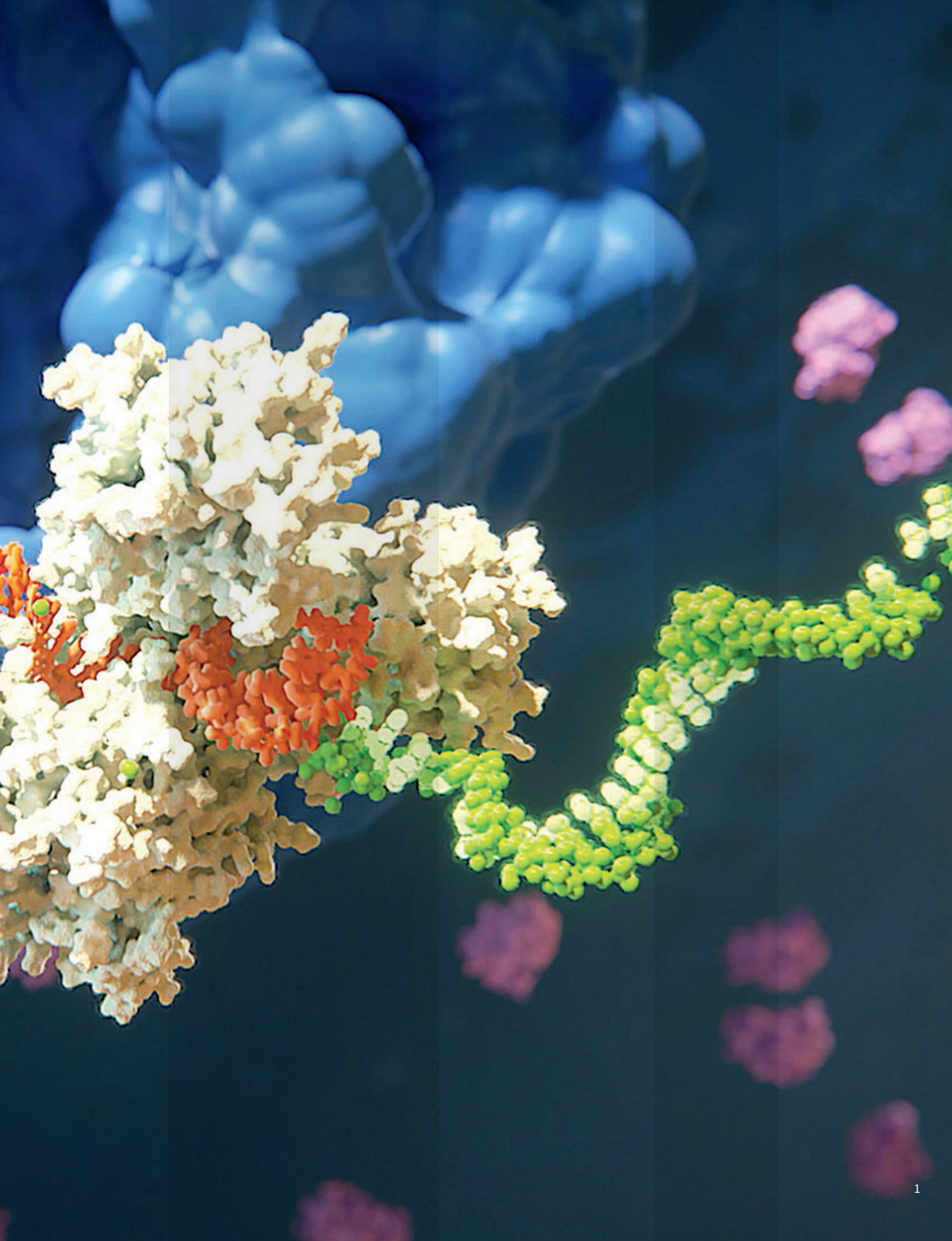
2020 ANNUAL REPORT

Alnylam® PHARMACEUTICALS

JOHN, DIAGNOSED WITH PRIMARY HYPEROXALURIA TYPE 1 (PH1), U.S.

UNBOUNDED INNOVATION

When Alnylam was founded, many deemed our goals “impossible,” “impractical” and “unrealistic” yet our innovative science proved the naysayers wrong. With the approval of our 3rd and 4th medicines—OXLUMO™ and Leqvio® (licensed to Novartis) in 2020, and exciting growth in our pipeline, we have furthered our reputation for unbounded innovation and cemented our leadership in RNAi therapeutics.



As we celebrate the approval of our medicines in new markets, and expand our workforce and operations around the world, we continue our unwavering focus on the needs of patients and helping them access our innovative therapies. They have been and will always be our North Star.

UNWAVERING **FOCUS**

CHEN, DIAGNOSED WITH HATTR AMYLOIDOSIS, AND HIS WIFE KALINE, BRAZIL

KYRA, ASSOCIATE SCIENTIST, U.S.

UNCOMPROMISING DEDICATION

As the pioneer in RNAi therapeutics, we have always been uncompromisingly dedicated to translating the breakthrough discovery of RNA interference (RNAi) into transformational medicines to help as many people as we can. As our advances allow us to begin to pivot toward diseases with larger patient populations, we believe that we are beginning to recognize the full potential of this new class of medicines.

BENSON, DIAGNOSED WITH PRIMARY HYPEROXALURIA TYPE 1 (PH1), U.S.

UNDENIABLE **IMPACT**

Alnylam exists to bring forward new treatments for patients in need who have limited or inadequate treatment options, like Benson, who is diagnosed with primary hyperoxaluria type 1 (PH1). The approval of OXLUMO™ (lumasiran), the first and only treatment for PH1, exemplifies our undeniable impact.

The Year We Fulfilled (and Exceeded) Our "Alnylam 2020" Vision and Goals

2020 was a year of remarkable accomplishments in the face of extraordinary challenges posed by the global pandemic; we not only fulfilled but exceeded our Alnylam 2020 vision and goals of building a multi-product, global biopharmaceutical company with a deep clinical pipeline and a robust, organic product engine to drive sustainable innovation and value creation. With four revenue-generating products, including most recently OXLUMO™ (lumasiran) and Leqvio® (inclisiran) in Europe with our partners at Novartis, a dozen programs in the clinic, including six in late stages of clinical development, we remained true to our **"Challenge Accepted"** mindset and exhibited our commitment to continue to innovate and produce important medicines for patients around the world in need.

We are extremely pleased with the commercial performance of ONPATTRO® (patisiran)—our first-in-class RNAi therapeutic for the treatment of polyneuropathy in adults with hereditary ATTR (hATTR) amyloidosis. ONPATTRO is now available across the globe—in the U.S., EU, Japan, Canada, Switzerland, Brazil and Israel, and achieved reimbursement in major EU countries faster than the average of all EMA-approved and reimbursed orphan drugs. By year end 2020, approximately 1,350 patients worldwide were receiving commercial drug, and we achieved global net product revenues of approximately $306 million for the year. In addition, we are continuing to advance patisiran in the APOLLO-B Phase 3 study in ATTR amyloidosis patients with cardiomyopathy. If successful, APOLLO-B could potentially enable label expansion for ONPATTRO in the 2022-2023 timeframe to include treatment of cardiomyopathy in patients with hereditary and wild-type ATTR amyloidosis.

> "Faced with a world and lives drastically upended by COVID-19, our people demonstrated incredible resilience and the fullest commitment to our mission of developing transformative medicines for patients."

Beyond ONPATTRO, we intend to create an ATTR franchise that also includes vutrisiran, our subcutaneously administered investigational RNAi therapeutic in development for the treatment of the polyneuropathy of hATTR amyloidosis and also in development for the treatment of ATTR amyloidosis. We recently reported positive topline results from

the Phase 3 HELIOS-A trial in patients with hATTR amyloidosis with polyneuropathy and are also evaluating vutrisiran in the HELIOS-B Phase 3 study in patients with ATTR cardiomyopathy, where we are collecting cardiovascular (CV) outcomes data. If positive, HELIOS-B could enable vutrisiran to enter the very large wild-type market with a label that could potentially include CV outcomes, providing us the opportunity to secure our leadership in the ATTR amyloidosis space.

With GIVLAARI® (givosiran)—our first GalNAc conjugated RNAi therapeutic to gain regulatory approval—we are pleased by the rising demand that we are seeing. GIVLAARI is now available in the U.S., Canada, EU, and Brazil. By year-end 2020, approximately 200 patients worldwide were receiving commercial drug, and we achieved global net product revenues of approximately $55 million for the year.

In 2020, two additional RNAi medicines, OXLUMO™ in the U.S. and in the EU and Leqvio® in the EU, entered the market, extending our commercial journey well beyond ONPATTRO and GIVLAARI.

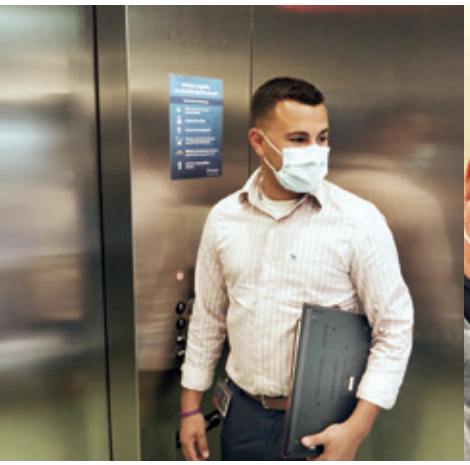
OXLUMO (lumasiran)—our RNAi therapeutic for the treatment of primary hyperoxaluria type 1 (PH1)—received back-to-back regulatory approvals from the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) in November. OXLUMO is now the first-ever FDA and EMA approved medicine for the treatment of PH1 and the first RNAi medicine that was evaluated for use in adults and young children, including infants. On the clinical front, we presented positive readouts from our ILLUMINATE-A (for patients age six and older) and ILLUMINATE-B (for patients under the age of six) Phase 3 pivotal studies of lumasiran demonstrating clinically significant and sustained reductions of urinary oxalate in patients across all age groups and completed enrollment in our ongoing ILLUMINATE-C Phase 3 study evaluating lumasiran in patients of all ages with advanced PH1, including patients on dialysis. Collectively, the ILLUMINATE program is designed to support the broad utility of lumasiran across the full spectrum of PH1 disease onset and severity.

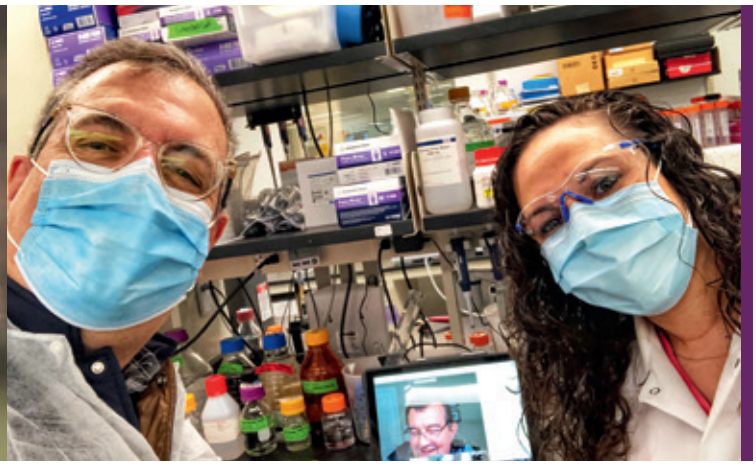
OXLUMO™ (lumasiran) for injection 94.5 mg/0.5 mL

In 2020, OXLUMO™ (lumasiran)—the world's first RNAi therapeutic to have been evaluated in both adults and children, including infants—was approved by the FDA to lower urinary oxalate levels in adult and pediatric patients with primary hyperoxaluria type 1 (PH1) and by the EMA for the treatment of PH1 patients of all age groups.

NOVARTIS

2020 also marked the approval of Leqvio® (inclisiran) in Europe by our partners at Novartis—the first siRNA (RNAi therapeutic) approved by the EMA with the potential to benefit millions of people with hypercholesterolemia around the world, validating the future potential of RNAi therapeutics in large population diseases.





A SIGNIFICANT NUMBER OF ALNYLAM EMPLOYEES CONTINUED TO WORK ON-SITE THROUGHOUT 2020

We also saw important advancements in our partnered programs. In December 2020, Novartis announced the approval of Leqvio (inclisiran)—the first and only siRNA therapy (or RNAi therapeutic) for the treatment of adults with hypercholesterolemia or mixed dyslipidemia—by the EMA. Importantly, the ORION program—designed to evaluate the safety and efficacy of inclisiran—represents the largest clinical experience for an RNAi therapeutic to date, providing a comprehensive overview of the safety profile from over 3,600 patients and for the first time showcasing the utility of the RNAi therapeutic platform in the context of a highly prevalent disease setting.

In addition, following a brief pause in dosing and enrollment due to a small number of nonfatal thrombotic adverse events, our partners at Sanofi have resumed dosing of adults and adolescents with fitusiran—in development for the treatment of hemophilia A or B, with or without inhibitors—in the ATLAS Phase 3 program. With the maturation of these partnered assets where we have a significant economic stake, we are excited by the potential for future royalty revenues.

With regard to our early-stage and preclinical assets, we have multiple important efforts ongoing across a variety of diseases including hypertension, non-alcoholic steatohepatitis (NASH), and complement-mediated diseases, as well as global diseases such as chronic hepatitis B virus infection and COVID-19. In particular, we are highly encouraged by the initial Phase 1 clinical data from our ALN-AGT program in development for the treatment of hypertension, where we have observed clinically meaningful reductions in blood pressure with an encouraging safety profile. Further, the durability profile of ALN-AGT may allow us to reimagine the treatment of hypertension with a potential quarterly or biannual dose regimen.

On the business front, we substantially strengthened our cash position, entering into a broad strategic financing collaboration with Blackstone—a leading private equity firm with a strong commitment to the life sciences—under which Alnylam will receive up to $2 billion. This deal—one of the largest financings in biotech history—provides Alnylam with very significant capital that, we believe, secures our path toward achieving a self-sustainable financial profile without the need to access the equity markets in the future.

There were also a number of exciting developments across our management team with appointments of new leaders including Tolga Tanguler as our Chief Commercial Officer. In addition, Yvonne Greenstreet assumed an expanded role as President and Chief Operating Officer, and we welcomed Dr. Olivier Brandicourt, former CEO of Sanofi, to the Company's Board of Directors. We believe these appointments more strongly position us to execute on our newly announced *Alnylam P^5 x 25* vision for the next stage of Alnylam's journey to become a top 5 independent, global biopharma company admired for its dedication to patients, corporate culture, scientific innovation, social responsibility, and commercial excellence.

Importantly, this year we put forth the pillars of our corporate social responsibility—our commitment to take on bold challenges that improve the health of humanity, acting every day as relentless advocates for science, patients, employees, communities and our planet. Our Patient Access Philosophy is consistent with that commitment where we hold ourselves accountable with a specific set of actions; our annual Patient Access Philosophy report details our progress and the steps we have taken as a company to ensure patients have access to the medicines that may benefit them. Our Diversity, Equity and Inclusion efforts demonstrate our commitment to employees and an inclusive work culture.

Relatedly, in 2020 we celebrated multiple notable recognitions by peers and the industry, including recognition by *The Boston Globe* as a Top Place to Work for the sixth year in a row; by *Science* magazine as a top biopharma employer for two consecutive years; the 2020 Prix Galien USA Award for Best Biotechnology Product for ONPATTRO® (patisiran); #3 ranking in gender parity and #1 in fair representation for Women of Color in Executive and Board Leadership, and among the top 25 employers in Massachusetts in the Eos Foundation's inaugural Women's Power Gap in Corporate Massachusetts Survey and Rankings.

In closing, I'd like to highlight that despite the many challenges associated with 2020, including an unprecedented global health crisis, this was a truly unforgettable year for Alnylam, a year when we came together to deliver on our ambitious goals, securing two regulatory approvals, achieving two positive Phase 3 readouts, filing a Clinical Trial Application (CTA) and surpassing 30 value-based agreements (VBAs) with payers across our marketed products, thus delivering value to patients, stockholders and employees alike. I am beyond grateful to our employees for their passion, hard work and untempered enthusiasm in such challenging times and to our stockholders for their continued support of Alnylam.

JOHN MARAGANORE, PHD | CHIEF EXECUTIVE OFFICER, ALNYLAM

ALNYLAM BY THE NUMBERS

4

Product Candidates Approved in Under 3 Years

50+

Countries with Active Clinical Trials

13

Programs in the Clinic

"Our growth during 2020 was made all the more remarkable by the conditions under which it happened. Despite COVID-19, our dedicated employees exceeded our goals for the year."

YVONNE GREENSTREET, MBCH, MBA | PRESIDENT & COO, ALNYLAM

ALNYLAM ACROSS THE GLOBE

ALNYLAM OFFICES ALNYLAM DISTRIBUTORS

Argentina
Austria
Belgium
Brazil
Canada
Czech Republic
Denmark
France
Germany
Ireland
Italy
Japan
Luxembourg
Netherlands
Portugal
Spain
Sweden
Switzerland
Taiwan
United Kingdom
United States

1,450+

Employees Worldwide

30 in **21**

Alnylam Offices Countries

ATTR AMYLOIDOSIS

"Today, having a daughter who is not a carrier, and waiting for my first grandson to be born is the greatest joy I have because this is a quick disease that does not forgive."

LIANA, DIAGNOSED WITH HATTR AMYLOIDOSIS, BRAZIL

Transthyretin (ATTR) amyloidosis is a rare, underdiagnosed, rapidly progressive, debilitating, and fatal disease caused by misfolded TTR that accumulates as amyloid fibrils in multiple tissues including the nerves, heart, and GI tract. There are two types of ATTR amyloidosis: hereditary (hATTR) amyloidosis and wild-type (wtATTR) amyloidosis.

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

2020 MILESTONES

- **Patisiran is currently being evaluated for efficacy and safety in patients with transthyretin-mediated (ATTR) amyloidosis with cardiomyopathy in the Phase 3 APOLLO-B study**
- **Filed for regulatory approval in Taiwan**

Vutrisiran An investigational, subcutaneously-administered RNAi therapeutic in development for the treatment of ATTR amyloidosis, which encompasses both hereditary and wild-type amyloidosis. It is designed to target and silence specific messenger RNA, blocking the production of wild-type and mutant TTR protein before it is made. Quarterly administration of vutrisiran may help to reduce deposition and facilitate the clearance of TTR amyloid deposits in tissues and potentially restore function to these tissues.

2020 MILESTONES

- **Positive topline results from the HELIOS-A Phase 3 study of vutrisiran in patients with hATTR amyloidosis with polyneuropathy were recently announced, and the Company plans to submit a New Drug Application with the U.S. FDA in early 2021**
- **HELIOS-B, a Phase 3 placebo-controlled mortality and cardiovascular events trial in patients with ATTR amyloidosis with cardiomyopathy, continues to enroll patients**

onpattro® (patisiran) lipid complex injection 10 mg/5 mL

KEY STATISTICS
AS OF Q4 2020

>90%
adherence on commercial ONPATTRO

~1,350
patients on commercial ONPATTRO

99%
U.S. lives with confirmed access to ONPATTRO, if prescribed

>20
countries outside U.S. where ONPATTRO has achieved market access

ACUTE HEPATIC PORPHYRIA

"I had to learn that you just have to keep going and rely on the support of the ones that love you, that keep encouraging you to take another step."

NATHAN, DIAGNOSED WITH ACUTE HEPATIC PORPHYRIA, U.S.

Acute hepatic porphyria (AHP) refers to a family of ultra-rare, genetic diseases characterized by debilitating, potentially life-threatening attacks and, for some patients, chronic manifestations that negatively impact daily functioning and quality of life. While severe, unexplained abdominal pain is the most common symptom of AHP, people may also experience nausea, vomiting, seizures, anxiety and depression, and pain in their limbs, back or chest.

AHP FACTS

- **In the U.S. and EU, ~1k people suffer frequent and severe AHP attacks and ~5k people experience one or more AHP attacks annually**
- **Severe, unexplained abdominal pain occurs in more than 90% of people who experience AHP attacks**
- **Patients with AHP can wait up to 15 years for a confirmed diagnosis**

GIVLAARI® (givosiran) is an RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) approved for the treatment of adults with AHP in the U.S., Brazil and Canada, and for the treatment of AHP in adults and adolescents aged 12 years and older in the EU.

2020 MILESTONES

- **Published pivotal results from the ENVISION Phase 3 study in *The New England Journal of Medicine***
- **Reported 18-month interim results from the ongoing open-label extension period of the ENVISION Phase 3 study, demonstrating sustained efficacy and safety with long-term dosing of GIVLAARI**
- **Received regulatory approvals in the EU, Brazil and Canada**
- **Filed for regulatory approvals in Switzerland, Israel and Japan**

GIVLAARI®
(givosiran) injection for subcutaneous use 189 mg/mL

KEY STATISTICS
AS OF Q4 2020

80%
of people with AHP are women

~200
patients worldwide on commercial GIVLAARI

94%
U.S. lives with confirmed access to GIVLAARI, if prescribed

10+
value-based agreements (VBAs) finalized

PRIMARY HYPEROXALURIA TYPE 1

"To know that your child has a genetic disease is disheartening. We want to do everything we can to support her, that's what drives us."

DAN, FATHER OF ELOISE VIOLA, DIAGNOSED WITH PRIMARY HYPEROXALURIA TYPE 1 (PH1), U.S.

Primary hyperoxaluria type 1 (PH1) is an ultra-rare, inherited disease in which an enzyme defect in the liver causes oxalate overproduction, resulting in recurrent kidney stones, progressive loss of kidney function and, ultimately, end-stage renal disease with subsequent accumulation of oxalate throughout the body, including the eyes, bones, skin and the heart.

PH1 FACTS

- **Majority of patients are diagnosed throughout childhood and adolescence, but patients can present with symptoms at any age, from infancy to late adulthood**
- **Kidney stones are the most common and early symptom**
- **Patients with advanced disease can face an aggressive dialysis regimen of 6-7 sessions per week**

OXLUMO™ (lumasiran) is an RNAi therapeutic targeting hydroxyacid oxidase 1 (HAO1) that encodes glycolate oxidase (GO), an enzyme upstream of the disease-causing defect in PH1. OXLUMO is approved in the U.S. for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients, and in the EU for the treatment of PH1 in all age groups. OXLUMO is the first-ever treatment for PH1 and the first RNAi medicine to have been evaluated in adults and children, including infants.

The safety and efficacy of lumasiran are being evaluated in the ILLUMINATE-C Phase 3 study in children and adults with advanced PH1, including patients on dialysis.

OXLUMO™ (lumasiran) for injection 94.5 mg/0.5 mL

2020 MILESTONES

- **Reported positive results from the ILLUMINATE-A study in patients six years of age and older**
- **Reported positive results from the ILLUMINATE-B study in patients under the age of six, including infants**
- **Completed enrollment in the ILLUMINATE-C study**
- **Received regulatory approvals in the U.S. and EU**
- **Received pediatric rare disease priority review voucher from FDA**
- **Filed for regulatory approval in Brazil**
- **Introduced enhanced value-based agreements (VBAs) with new patient need adjustment (PNA)**

KEY STATISTICS
AS OF Q4 2020

~65%
of PH1 patients remain undiagnosed until they progress to end-stage renal disease

1,300-2,100
patients with a confirmed PH1 diagnosis in the U.S. and EU

~6 yrs
mean time to diagnosis in adults

>1 gal
average daily intake of water patients need to consume to help reduce kidney stone formation

5
value-based agreements (VBAs) executed, as of mid March 2021

19
start forms submitted to initiate treatment with OXLUMO

OUR PIPELINE

Alnylam's robust clinical development pipeline is focused on four strategic therapeutic areas (STArs) targeting rare and more prevalent diseases. It features six programs in late-stage development.

Focused in 4 Strategic Therapeutic Areas

● Genetic Medicines ● Cardio-Metabolic Diseases
● Infectious Diseases ● CNS/Ocular Diseases

PRODUCT/PROGRAM	DISEASE	HUMAN POC[1]	BREAKTHROUGH DESIGNATION	EARLY/MID STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[2]	COMMERCIAL RIGHTS
ONPATTRO® (patisiran)[3]	*Hereditary ATTR Amyloidosis*	✓	✓			●	Global
GIVLAARI® (givosiran)[4]	*Acute Hepatic Porphyria*	✓	✓			●	Global
OXLUMO™ (lumasiran)[5]	*Primary Hyperoxaluria Type 1*	✓	✓			●	Global
Leqvio® (inclisiran)[6]	*Hypercholesterolemia*	✓				●	Milestones & up to 20% Royalties[7]
Patisiran	*ATTR Amyloidosis Label Expansion*	✓			●		Global
Vutrisiran	*ATTR Amyloidosis*	✓			●		Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	✓			●		15-30% Royalties
Lumasiran	*Severe PH1 Recurrent Renal Stones*	✓		●	●		Global
Cemdisiran	*Complement-Mediated Diseases*	✓		●			50-50
Cemdisiran/ Pozelimab[8]	*Complement-Mediated Diseases*			●			Milestone/ Royalty
ALN-AAT02 (DCR-A1AT)[9]	*Alpha-1 Liver Disease*	✓		●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	✓		●			50-50 option post-Phase 2
ALN-AGT	*Hypertension*	✓		●			Global
ALN-HSD[10]	*NASH*			●			50-50
ALN-COV (VIR-2703)[10]	*COVID-19*			○			50-50 option post-Phase 2

[1] POC, proof of concept—defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2] Includes marketing application submissions
[3] Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland, Brazil and Taiwan 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
[4] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older
[5] Approved in the U.S. for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients, and in the EU for the treatment of PH1 in all age groups
[6] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran
[7] 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam
[8] 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
[9] Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development
[10] Potential 2021 IND candidate

JEAN-CHRISTOPHE, DIAGNOSED WITH HATTR AMYLOIDOSIS, FRANCE

STRATEGIC COLLABORATIONS

We seek out partners who share our passion for innovation, strive to make a significant impact in the lives of patients and who can help us advance RNAi therapeutics across therapeutic areas. Our partnerships range from financing to commercialization to development to preclinical research and genetics.

REGENERON

VIR

SANOFI

Blackstone

NOVARTIS

biobank

SUPPORTING PATIENTS AND HEALTHCARE PROFESSIONALS

Patients are at the core of everything we do. Alnylam was founded to help those people who lack adequate treatment options live fuller, healthier lives. Their needs inspire us to innovate and take action and their stories keep us focused on that goal.

At Alnylam, we all live by a shared philosophy when it comes to patient access: our innovative therapies must get to those who may benefit from them. That philosophy of putting the patient first isn't just a belief common among our leadership and employees, it's a statement of intent and a specific set of actions that we've undertaken as a company. Our Patient Access Philosophy was created before our first medicine was approved. It is our North Star, guiding how we embrace the need for innovation in addressing coverage delays or barriers and the decisions we make to ensure that patients around the world can access every medicine we develop.

Our Patient Access Philosophy has three pillars: **Help Patients, Deliver Value to Payers** and **Be Proactive and Accountable.**

Learn more about our commitment to patient access and download our 2020 Patient Access Philosophy Report at alnylam.com/access or by scanning this code with your mobile phone.

PATIENT ACCESS BY THE NUMBERS

>30

value-based agreements (VBAs) signed in the U.S.

>1,500

patients worldwide receiving commercial Alnylam therapies

zero price increases to date on two launched products

GLAUCIENE, DIAGNOSED WITH AHP, BRAZIL

PATIENT ACCESS AND DIAGNOSIS PROGRAMS

Alnylam ASSIST®

Alnylam Assist® is our patient support program for patients living in the U.S. and Canada prescribed one of our therapies, and their caregivers. Alnylam Assist provides support throughout the treatment journey including help understanding insurance coverage, options for financial support and educational materials and resources. Patients have a dedicated Case Manager to help make their experience more personalized.

AlnylamAct®

Alnylam Act® offers eligible patients in the U.S., Canada and Brazil with no-charge, 3rd-party genetic testing and counseling. Alnylam Act was developed to help reduce barriers to genetic testing and counseling to help facilitate accurate diagnosis and help patients make informed decisions about their health with their healthcare provider. Healthcare professionals or patients who use this program have no obligation to recommend, purchase, order, prescribe, promote, administer, use, or support any Alnylam product.

>700

patients enrolled in Alnylam Assist

>30k

genotyped samples through Alnylam Act

CORPORATE RESPONSIBILITY

Stemming from the core values of Alnylam, our approach to corporate responsibility (CR) embodies our **"Challenge Accepted"** philosophy. Our CR mission statement—**"Accepting Challenges to Improve the Health of Humanity"**—helps articulate how we approach our work each day. It describes our commitment to tackling unprecedented and complex challenges, taking courageous action, and using our business as a force for good.

Our CR efforts are focused in five key areas, each with dedicated leadership and specific goals and metrics by which we will evaluate our progress and impact annually.

JON, SCIENTIST, U.S.

PATIENTS

We strive to improve patients' lives and enable access to potentially life-changing treatments.

SCIENCE

We advocate for science and innovation to address critical health and social issues.

EMPLOYEES

We foster an open, diverse culture where employees feel included, supported, and heard.

COMMUNITY

We actively engage people in tackling the world's most pressing community and health equity challenges.

PLANET

We seek to improve the health and sustainability of our planet.

Learn more about Corporate Responsibility at Alnylam and download our 2020 CR Summary at alnylam.com/responsibility or by scanning this code with your mobile phone.

RECOGNITION

Our dynamic culture, exciting science and focus on diversity, equity and inclusion has made us a recognized leading employer. At Alnylam, we know that our long-term success and ability to deliver innovative medicines to patients require a highly motivated, diverse and inclusive workforce. We are committed to building a work environment with a shared mission and values and in which all employees feel they belong and are enabled to achieve their full potential. This focus on our people has made us an employer of choice around the world.

The Boston Globe TOP PLACES TO WORK 2015–2020

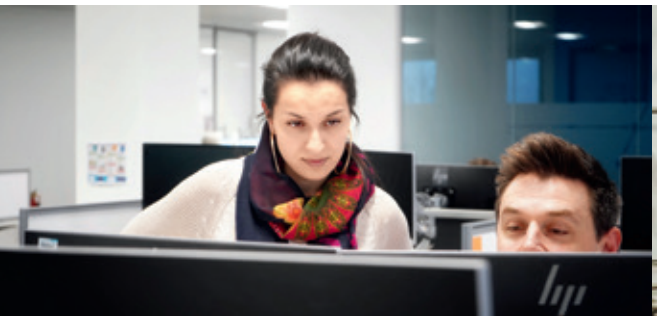
Science 2020 TOP EMPLOYER

Best Workplaces™ Great Place To Work. UK and Switzerland 2020

Employee Voice Award

Women's Power Gap Eos Foundation GENDER PARITY NOW

"Alnylam is a clear leader" —EOS FOUNDATION



"We are extremely proud of the high-functioning, open and inclusive culture we've built. It makes us a magnet for the very best talent and a place where people thrive, which in turn enables us to deliver on our mission of bringing innovative medicines to patients as quickly as possible."

KELLEY BOUCHER | CHIEF HUMAN RESOURCE OFFICER, ALNYLAM

ALNYLAM 2020 FORM 10-K

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, 2020

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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. Yes ☑ No ☐

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

The aggregate market value of the registrant's common stock, $0.01 par value per share ("Common Stock"), held by non-affiliates of the registrant, based on the last sale price of the Common Stock at the close of business on June 30, 2020, was $16,993,028,024. 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 5, 2021, the registrant had 117,002,019 shares of Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2021 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, 2020, 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, 2020
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"Alnylam," ONPATTRO®, GIVLAARI®, OXLUMO™, Alnylam Act® and Alnylam Assist® are trademarks and 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.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This annual report on Form 10-K contains forward-looking statements within the meaning of the federal securities laws, Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. We intend these forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995 and are including this statement for purposes of complying with those safe harbor provisions. All statements other than statements of historical facts contained in this annual report on Form 10-K are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "may," "will," "should," "could," "expects," "plans," "intends," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- risks related to the direct or indirect impact of the COVID-19 global pandemic, emerging or future variants of COVID-19 or any future pandemic, such as the scope and duration of the pandemic, government actions and restrictive measures implemented in response, the broad availability of safe and effective vaccine(s), material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by our products, or in patient enrollment in clinical trials, potential clinical trial, regulatory review and inspection or supply chain disruptions, and other potential impacts to our business, the effectiveness or timeliness of steps taken by us to mitigate the impact of the pandemic, and our ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic;
- our views with respect to the potential for RNAi therapeutics and investigational therapeutics, including ONPATTRO, GIVLAARI, OXLUMO, Leqvio®, vutrisiran and fitusiran;
- our plans for additional global regulatory filings and the continuing product launches of ONPATTRO, GIVLAARI, OXLUMO and our partner's plans with respect to Leqvio (inclisiran);
- our expectations regarding the advancement by our partner of inclisiran through United States, or U.S., regulatory review and toward the market;
- our expectations regarding potential market size for, and the successful commercialization of, ONPATTRO, GIVLAARI, OXLUMO, Leqvio (inclisiran) or any future products, including vutrisiran;
- our ability to obtain and maintain regulatory approvals and pricing and reimbursement for ONPATTRO, GIVLAARI, OXLUMO or any future products, including vutrisiran, and our partner's ability with respect to Leqvio (inclisiran);
- the progress of our research and development programs;
- our current and anticipated clinical trials and expectations regarding the reporting of data from these trials;
- the timing of regulatory filings and interactions with or actions or advice of regulatory authorities, which may affect the design, initiation, timing, continuation and/or progress of clinical trials or result in the need for additional pre-clinical and/or clinical testing or the timing or likelihood of regulatory approvals;
- the status of our manufacturing operations and any delays, interruptions or failures in the manufacture and supply of ONPATTRO, GIVLAARI, OXLUMO, or any of our product candidates (or product candidates being developed and commercialized by our partners) by our or their contract manufacturers or by us or our partners;
- our progress continuing to build and leverage global commercial infrastructure;
- our ability to successfully expand the indication for ONPATTRO in the future;
- the possible impact of any competing products on the commercial success of ONPATTRO, GIVLAARI, OXLUMO and Leqvio, as well as our product candidates, and, our, or with respect to Leqvio (inclisiran) or fitusiran, our partners', ability to compete against such products;
- our ability to manage our growth and operating expenses;
- our views and plans with respect to our 5-year *Alnylam* P^5x25 strategy, and our intentions to achieve the metrics associated with this strategy, including to become a top five biotech company in market capitalization by the end of 2025;
- our belief that the funding provided by our strategic financing collaboration with The Blackstone Group Inc., or Blackstone, and certain of its affiliates should enable us to achieve a self-sustainable profile without the need for future equity financing;

- our expectations regarding the length of time our current cash, cash equivalents and marketable securities will support our operations based on our current operating plan;
- our dependence on third parties for development, manufacture and distribution of products;
- our expectations regarding our corporate collaborations, including potential future licensing fees and milestone and royalty payments under existing or future agreements;
- obtaining, maintaining and protecting our intellectual property;
- our ability to attract and retain qualified key management and scientists, development, medical and commercial staff, consultants and advisors;
- the outcome of litigation or other legal proceedings;
- the risk of government investigations;
- regulatory developments in the U.S., and foreign countries;
- the impact of laws and regulations;
- developments relating to our competitors and our industry; and
- other risks and uncertainties, including those listed under the caption Part I, Item 1A, "Risk Factors" of this annual report on Form 10-K.

The risks set forth above are not exhaustive. Other sections of this annual report on Form 10-K may include additional factors that could adversely affect our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time and it is not possible for management to predict all risk factors, nor can we assess the impact of all risk factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements. Any forward-looking statements in this annual report on Form 10-K reflect our current views with respect to future events and with respect to our business and future financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those described under Part I, Item 1A, "Risk Factors" and elsewhere in this annual report on Form 10-K. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future. You are advised, however, to consult any further disclosure we make in our reports filed with the SEC.

This annual report on Form 10-K may include data that we obtained from industry publications and third-party research, surveys and studies. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. This annual report on Form 10-K also may include data based on our own internal estimates and research, including estimates regarding the impact of the COVID-19 pandemic (or related pandemic caused by coronavirus variants) on our financial statements and business operations. Our internal estimates have not been verified by any independent source and, while we believe any data obtained from industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data. Such third-party data, as well as our internal estimates and research, are subject to a high degree of uncertainty and risk due to a variety of factors, including those described in Part I, Item 1A, "Risk Factors" and elsewhere in this annual report on Form 10-K. These and other factors could cause our results to differ materially from those expressed in this annual report on Form 10-K.

SUMMARY OF MATERIAL RISKS ASSOCIATED WITH OUR BUSINESS

Our business is subject to numerous risks and uncertainties that you should be aware of before making an investment decision, including those highlighted in the section entitled "Risk Factors." These risks include, but are not limited to, the following:

Business Related Risks – Risks Related to Our Financial Results

- The current pandemic of the novel coronavirus, or COVID-19, and the future outbreak of other highly infectious or contagious diseases, could have a material adverse impact on our business, financial condition and results of operations, including our commercial operations and sales, clinical trials and pre-clinical studies.
- We are an early-stage commercial company and the marketing and sale of ONPATTRO, GIVLAARI, OXLUMO or any future products may be unsuccessful or less successful than anticipated.
- We have a history of losses and may never become and remain consistently profitable.
- We will require substantial funds to continue our research, development and commercialization activities.
- Although we sold a portion of the expected royalty stream and commercial milestones related to global sales of Leqvio by Novartis AG, or Novartis, we are entitled to retain the remaining portion of such future royalties and, if certain specified thresholds are met, to the remaining portion of commercial milestone payments, and any negative developments related to Leqvio (inclisiran), such as a delay in the expected timing of the resubmission by Novartis of the New Drug Application, or NDA, for inclisiran, could have a material adverse effect on the timing or amount of those payments.

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 certain of our product candidates.
- If any collaborator materially amends, terminates or fails to perform its obligations under agreements with us, the development and commercialization of our certain of product candidates could be delayed or terminated and we could suffer other economic harm.
- 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 rely on third parties to conduct our clinical trials, and if they fail to fulfill their obligations, our development plans may be adversely affected.

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 may have difficulty expanding our operations successfully as we continue our evolution 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.

Industry Related Risks – Risks Related to Development, Clinical Testing and Regulatory Approval of Our Product Candidates and the Commercialization of Our Approved Products

- 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.
- We or our partners may be unable to obtain U.S. or foreign regulatory approval for our or our partnered product candidates.
- Even if we or our partners obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory oversight.
- Even if we receive regulatory approval to market our product candidates, and our collaborators receive regulatory approval to market product candidates discovered by us or developed with our technology, the market may not be receptive to such product candidates upon their commercial introduction, which could prevent us from becoming profitable.
- 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 our commercial efforts may not be successful.

- The patient populations suffering from hereditary transthyretin-mediated amyloidosis, or hATTR amyloidosis, acute hepatic porphyria, or AHP and primary hyperoxaluria type 1, or PH1 are small and have not been established with precision.
- 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.
- Any drugs we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, thereby harming our business.
- Governments outside the U.S. may impose strict price controls, and the U.S. government may impose price controls or reference pricing, which may adversely affect our revenues.

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.
- 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.
- Other companies or organizations may challenge our patent rights or may assert patent rights that prevent us from developing and commercializing our products.
- 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.
- 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.

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 or our collaborators develop.
- We face competition from other companies that are working to develop novel drugs and technology platforms using technology similar to ours.

Risks Related to Our Common Stock

- If our stock price fluctuates, purchasers of our common stock could incur substantial losses.
- We may incur significant costs from class action litigation.
- 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.
- Regeneron’s ownership of our common stock could delay or prevent a change in corporate control.

The summary risk factors described above should be read together with the text of the full risk factors below, in the section entitled "Risk Factors" and the other information set forth in this annual report on Form 10-K, including our consolidated financial statements and the related notes, as well as in other documents that we file with the SEC. The risks summarized above or described in full below are not the only risks that we face. Additional risks and uncertainties not precisely known to us, or that we currently deem to be immaterial may also materially adversely affect our business, financial condition, results of operations and future growth prospects.

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 rare and prevalent diseases. To date, our efforts to advance this revolutionary approach have yielded the approval of four first-in-class RNAi-based medicines, ONPATTRO® (patisiran), GIVLAARI® (givosiran), OXLUMO™ (lumasiran) and Leqvio® (inclisiran).

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 N-acetylgalactosamine (GalNAc) conjugate approach or lipid nanoparticle (LNP) 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. During 2020, we also advanced approaches for lung delivery of siRNAs. 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.

In 2015, we charted our *Alnylam 2020* goals of building a multi-product, global commercial company with a deep clinical pipeline for future growth and an organic product engine for sustainable innovation and a great potential for patient impact. We ended 2020 exceeding these goals, with four marketed products and 12 clinical programs, including six in late-stage development, across four Strategic Therapeutic Areas, or "STArs:" Genetic Medicines; Cardio-Metabolic Diseases; Hepatic Infectious Diseases; and CNS/Ocular Diseases. Three of our marketed products are within the Genetic Medicines STAr, ONPATTRO, GIVLAARI and OXLUMO. ONPATTRO is approved by the United States Food and Drug Administration, or FDA, for the treatment of the polyneuropathy of hATTR amyloidosis in adults and has also been approved in the European Union, or EU, for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy, in Japan for the treatment of transthyretin, or TTR, type familial amyloidosis with polyneuropathy, and in several additional countries, including Brazil. Regulatory filings in other territories are pending and additional filings are planned for 2021 and beyond. GIVLAARI is approved in the U.S. for the treatment of adults with AHP in the EU for the treatment of AHP in adults and adolescents aged 12 years and older, and in Brazil and Canada for the treatment of AHP in adults. We have also filed for regulatory approval for givosiran (the non-branded drug name for GIVLAARI) in Switzerland and Japan and additional regulatory filings are pending or planned for 2021 and beyond. In November 2020, we received regulatory approval for OXLUMO in the U.S. and EU for the treatment of PH1 in all age groups. Regulatory filings in other territories are pending and additional filings are planned for 2021 and beyond.

Our fourth product, Leqvio (inclisiran), is being developed and commercialized by our partner Novartis, and recently received marketing authorization from the European Commission, or EC, for the treatment of adults with hypercholesterolemia or mixed dyslipidemia and is in the Cardio-Metabolic Diseases STAr. With respect to regulatory review by the FDA of the NDA filed with the FDA for inclisiran, the FDA issued a complete response letter on December 18, 2020, due to unresolved facility inspection-related conditions at a third-party manufacturing facility in Europe. Novartis is working closely with the third-party manufacturer and the FDA to obtain approval as soon as possible, and has guided for a resubmission of its NDA for inclisiran in Q2-Q3 2021.

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 name for GIVLAARI) for the treatment of adolescent patients with AHP; lumasiran (the non-branded name for OXLUMO) for the treatment of advanced PH1 and recurrent renal stones; patisiran (the non-branded drug name for ONPATTRO) for the treatment of transthyretin amyloidosis, or ATTR amyloidosis, with cardiomyopathy; vutrisiran for the treatment of ATTR amyloidosis; inclisiran (the non-branded name for Leqvio) for the treatment of atherosclerotic cardiovascular disease, or ASCVD, is being advanced by our partner Novartis; as well as fitusiran for the treatment of hemophilia, which is being advanced by our partner Sanofi Genzyme, the specialty care global business unit of Sanofi.

In early 2021, we launched our *Alnylam* P^5x25 strategy which focuses on our planned transition to a top five biotech company, as measured by market capitalization, by the end of 2025. With *Alnylam* P^5x25, we aim to deliver transformative rare and prevalent disease medicines for patients around the world through sustainable innovation, delivering exceptional financial performance and driving profitability. Specifically, we intend to end 2025 with the following profile:

Patients: Over 0.5 million on our RNAi therapeutics globally
Products: Six or more marketed products in rare and prevalent diseases

Pipeline: Over 20 clinical programs, with 10 or more in late stages and four or more INDs per year
Performance: ≥40% revenue CAGR (compound annual growth rate) through YE 2025
Profitability: Achieve sustainable non-GAAP (generally accepted accounting principles) profitability within the period

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, Novartis (which acquired our partner The Medicines Company, or MDCO, in 2020), Sanofi Genzyme, Vir Biotechnology, Inc., or Vir, and Dicerna Pharmaceuticals, Inc., or Dicerna.

The COVID-19 Pandemic

In March 2020, the World Health Organization declared the outbreak of a novel strain of coronavirus, or COVID-19, as a pandemic, which continues to spread or resurge throughout the U.S. and worldwide. We could be materially and adversely affected by the risks, or the public perception of the risks, related to an epidemic, pandemic, outbreak, or other public health crisis, such as the current COVID-19 pandemic. We are continuing to monitor the global pandemic and spread of COVID-19 and plan to continue taking steps to identify and mitigate the adverse impacts on, and risks to, our business posed by its spread and actions taken by governmental and health authorities to address the COVID-19 pandemic. The spread of COVID-19 has caused us to modify our business practices, including implementing a global work from home policy for all employees who are able to perform their duties remotely and restricting all nonessential business travel, and we expect to continue to take actions as may be required or recommended by government authorities or as we determine are in the best interests of our employees, the patients we serve and other business partners in light of COVID-19 and variants thereof. Where and to the extent permitted to be open under local regulations, our office sites are operational with physical distancing, temperature screening, contact tracing and cleaning measures in place, as well as voluntary testing protocols in our Massachusetts facilities. At this time, we cannot predict when certain restrictions that are in place to protect our employees can be safely reduced or will no longer be needed, and such restrictions are likely to remain in place until there is widespread availability and distribution of COVID-19 vaccines. Due to the speed and fluidity with which the COVID-19 pandemic continues to evolve, and the emergence of highly contagious variants, we do not yet know the full extent of the impact of COVID-19 and SARS-CoV-2 on our business operations. The ultimate extent of the impact of any epidemic, pandemic, outbreak, or other public health crisis on our business, financial condition and results of operations will depend on future developments, which are highly uncertain and cannot be predicted, including new information that may emerge concerning the severity of such epidemic, pandemic, outbreak, or other public health crisis and actions taken to contain or prevent the further spread, including the availability and efficacy of vaccines, among others. Accordingly, we cannot predict the extent to which our business, financial condition and results of operations will be affected. We remain focused on maintaining a strong balance sheet, liquidity and financial flexibility and continue to monitor developments as we deal with the disruptions and uncertainties from a business and financial perspective relating to COVID-19 and variants thereof. We will continue to work diligently with our partners and stakeholders to support patient access to our approved medicines, advance our product candidates under regulatory review as well as in our clinical studies to the extent safe to do so for patients, caregivers and healthcare practitioners, and ensure the continuity of our manufacturing and supply chain. For additional information related to the actual or potential impacts of COVID-19 on our business, please read Part I, Item 1A, "Risk Factors" of this annual report on Form 10-K.

Key 2020 and Recent Highlights

TTR Franchise

- ***ONPATTRO (patisiran) – hATTR Amyloidosis with Polyneuropathy***
  - Recognized ONPATTRO global net revenue of $306.1 million for the year ended December 31, 2020
  - Attained approximately 1,350 patients worldwide on commercial ONPATTRO treatment as of December 31, 2020
  - Received regulatory approvals in Brazil, Israel and Taiwan
  - Achieved market access in over 20 countries
- ***Patisiran – ATTR Amyloidosis with Cardiomyopathy***
  - Continued enrollment in the APOLLO-B Phase 3 study in ATTR amyloidosis patients with cardiomyopathy, with plans to complete enrollment in early 2021
- ***Vutrisiran (ALN-TTRsc02) – ATTR Amyloidosis***
  - Reported positive topline results from the HELIOS-A Phase 3 study of vutrisiran in hATTR amyloidosis with polyneuropathy, with plans to file an NDA with the FDA in early 2021
  - Continued enrollment in the HELIOS-B Phase 3 study in ATTR amyloidosis patients with cardiomyopathy

- Announced potential for a biannual dosing regimen option with plans to initiate a clinical trial of this dosing regimen in early 2021

Commercial/Late-Stage Pipeline

- ***GIVLAARI (givosiran) – Acute Hepatic Porphyria***
  - Recognized GIVLAARI global net revenue of $55.1 million for the year ended December 31, 2020
  - Attained approximately 200 patients worldwide on commercial GIVLAARI treatment as of December 31, 2020
  - Received regulatory approvals in the EU, Brazil and Canada
- ***OXLUMO (lumasiran) – Primary Hyperoxaluria Type 1***
  - Received regulatory approval for OXLUMO in the U.S. and EU
  - Achieved global net product revenues for the fourth quarter of approximately $0.3 million representing initial patient demand in Europe
  - Reported positive topline results and six-month primary analysis results for the ILLUMINATE-B Phase 3 pivotal study in patients younger than six years of age with preserved renal function
  - Completed enrollment in the ILLUMINATE-C Phase 3 study of lumasiran in patients of all ages with advanced PH1, with plans to report topline results in mid-2021
- ***Leqvio (inclisiran) – Hypercholesterolemia (in collaboration with Novartis)***
  - Our partner, Novartis, received marketing authorization for Leqvio from the EC in December 2020
  - Novartis received a complete response letter from the FDA in December 2020, due to unresolved facility inspection-related conditions at a third-party manufacturing facility in Europe; Novartis is working closely with the third-party manufacturer and the FDA to obtain approval as soon as possible, and has guided for a resubmission of its NDA in Q2-Q3 2021
- ***Fitusiran - Hemophilia (in collaboration with Sanofi Genzyme)***
  - Continued advancement of the ATLAS Phase 3 program for fitusiran in patients with hemophilia A or B with and without inhibitors; following an assessment of available data and alignment with several health authorities, including the FDA, Sanofi Genzyme resumed fitusiran dosing in ongoing adolescent and adult studies in certain countries with protocol amendments to address adjustments to dose and dosing regimen

Early-Stage and Pre-Clinical Pipeline

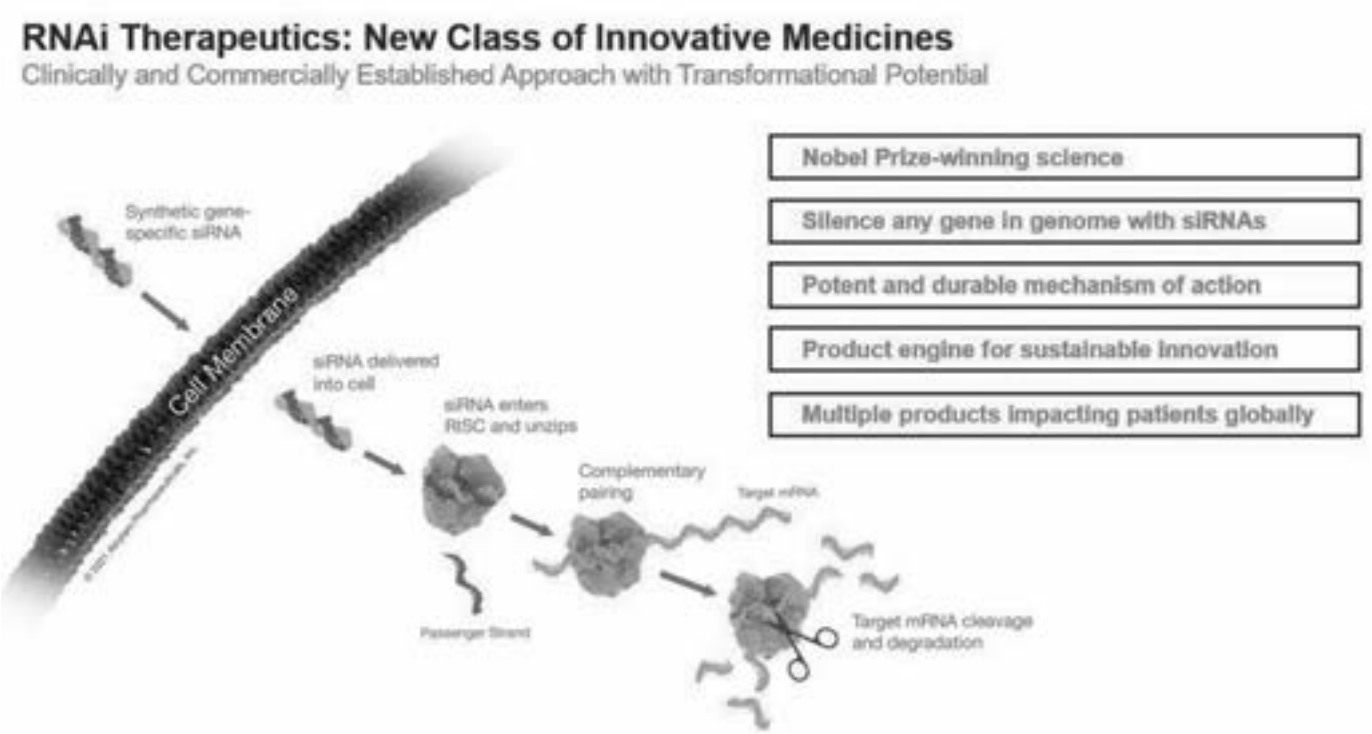
- ***Cemdisiran*** for the treatment of complement-mediated diseases; continued enrollment and dosing in the Phase 2 study in IgA nephropathy, and initiated dosing in a Phase 1 study of combination therapy with pozelimab, an anti-C5 monoclonal antibody, in collaboration with Regeneron
- ***ALN-AGT*** for the treatment of hypertension; presented positive interim results from the Phase 1 study of ALN-AGT
- ***ALN-HBV02*** (VIR-2218) for the treatment of chronic hepatitis B virus, or HBV, infection; Vir presented positive interim results from a Phase 2 study of patients with chronic HBV infection and continued enrollment and dosing in a Phase 2 combination trial of VIR-2218 with pegylated interferon-alpha (PEG-IFN-α)
- ***ALN-HSD*** for the treatment of nonalcoholic steatohepatitis, or NASH; initiated dosing in Phase 1 study with the program to advance in collaboration with Regeneron
- ***ALN-COV*** (Vir-2703) for the treatment and/or prevention of COVID-19; selected a development candidate under collaboration with Vir
- ***ALN-APP*** for the treatment of cerebral amyloid angiopathy and autosomal dominant Alzheimer's Disease; selected a development candidate with Regeneron electing to opt-in to program co-development and an expected clinical trial application, or CTA, filing in mid-2021

Corporate Highlights

- ***Finance***
  - Ended 2020 with $1.87 billion in cash, cash equivalents and marketable securities
- ***Business***
  - Entered into a strategic financing collaboration with certain affiliates of Blackstone, under which we will receive up to $2 billion in financing; closed $150 million R&D funding component

- Expanded exclusive licensing agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases to include the development and commercialization of RNAi therapeutics targeting SARS-CoV-2 and up to three additional targets focused on human host factors for SARS-CoV-2
- Entered into a development and commercialization collaboration with Dicerna, to develop and commercialize investigational RNAi therapeutics for the treatment of alpha-1 antitrypsin deficiency-associated liver disease, or alpha-1 liver disease, and completed a non-exclusive cross-licensing agreement with Dicerna regarding the companies' respective intellectual property for our lumasiran and Dicerna's nedosiran programs for the treatment of primary hyperoxaluria

RNAi Therapeutics – A New Class of Innovative Medicines



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 enabled execution on our *Alnylam 2020* strategy and we expect this success will further enable us to achieve our *Alnylam* P^5x25 strategy under which we expect to sustainably and organically create and commercialize transformative rare and common disease medicines benefiting hundreds of thousands of patients around the world while delivering strong financial performance and profitability, resulting in a leading biotech profile by the end of 2025.

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 and is associated with potent, rapid and durable target gene silencing and an encouraging tolerability profile in clinical studies conducted to date, as well as in our commercial experience. 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, OXLUMO, and Leqvio, our recently approved medicines. 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-HBV02, ALN-AGT and ALN-HSD, are in the clinic, with what we believe are 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 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. In 2020, we also began to advance lung delivery of RNAi therapeutics directed to the SARS-COV-2 genome in collaboration with our partners at Vir.

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 four commercially approved products, providing strong support for our approach to drug development. Moreover, we believe that our reproducible and modular platform will support our *Alnylam* P^5x25 *s*trategy under which we expect to sustainably and organically create and commercialize transformative rare and common disease medicines benefiting hundreds of thousands of patients around the world while delivering strong financial performance and profitability, resulting in a leading biotech profile by the end of 2025.

Our Product Pipeline

Our broad pipeline, including four 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, European Medicines Agency, or EMA, or any other health authority and no conclusions can or should be drawn regarding the safety or efficacy of these investigational therapeutics.

The chart below is a summary of our commercial products and late- and early-stage development programs as of January 31, 2021. It identifies those programs for which we have received marketing approval, the stage of our programs and our commercial rights to such programs:

Focused in 4 Strategic Therapeutic Areas (STArs):
Genetic Medicines · Cardio-Metabolic Diseases · Infectious Diseases · CNS/Ocular Diseases

		EARLY/MID-STAGE (IND/CTA Filed-Phase 2)	LATE STAGE (Phase 2-Phase 3)	REGISTRATION/ COMMERCIAL[1] (OLE/Phase 4/BLA/registrations)	COMMERCIAL RIGHTS
onpattro	*hATTR Amyloidosis*[2]			●	Global
GIVLAARI	*Acute Hepatic Porphyria*[3]			●	Global
OXLUMO	*Primary Hyperoxaluria Type 1*[4]			●	Global
Leqvio[5] (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[5]
Patisiran	*ATTR Amyloidosis*		●		Global
Vutrisiran	*ATTR Amyloidosis*		●		Global
Fitusiran	*Hemophilia*		●		15-30% Royalties
Lumasiran	*Severe PH1 Recurrent Renal Stones*	●	●		Global
Cemdisiran	*Complement-Mediated Diseases*	●			50-50
Cemdisiran/Pozelimab Combo[6]	*Complement-Mediated Diseases*	●			Milestone/Royalty
ALN-AAT02 (DCR-A1AT)[7]	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[8]	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
ALN-AGT	*Hypertension*	●			Global
ALN-HSD	*NASH*	●			50-50

[1] Includes marketing application submissions; [2] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S. and EU for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [6] Cemdisiran and pozelimab are each currently in Phase 2 development. Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [7] Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development; [8] Vir is leading and funding development of ALN-HBV02.

As indicated in the chart above, to date we have received marketing approval for ONPATTRO, GIVLAARI and OXLUMO, and Novartis has received approval for Leqvio, 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 in TTR gene) or nonhereditary (ageing) causes, respectively. In ATTR amyloidosis, misfolded TTR proteins accumulate as amyloid fibrils in multiple organs

and tissue types. hATTR amyloidosis can include sensory and motor neuropathy, autonomic neuropathy 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 improve 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, Switzerland, Brazil and Israel, 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 other territories are currently under review and additional filings are planned for 2021.

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; specific Orphan Drug Designations vary by country/region.

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, with enrollment expected to be completed in early 2021. 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 change from baseline in 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. Quarterly, or perhaps biannual, administration of vutrisiran may help to reduce the deposition and facilitate the clearance of TTR amyloid deposits in tissues like the nerves, heart and gastrointestinal tract; this reduction and clearance may potentially restore function. In January 2021, we reported positive topline results from our HELIOS-A Phase 3 study of vutrisiran in patients with hATTR amyloidosis with polyneuropathy, and announced our intention to submit an NDA for vutrisiran with the FDA in early 2021, with regulatory filings following in additional countries, including Brazil and Japan. Upon obtaining results from the 18-month analysis of HELIOS-A, expected in late 2021, we plan to submit a marketing authorisation application, or MAA, in the EU as previously aligned with the EMA. To date, vutrisiran has received both U.S. and EU Orphan Drug Designations; specific Orphan Drug Designations indications vary by country/region.

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 enrolled 164 patients with hATTR amyloidosis with polyneuropathy at 57 sites in 22 countries. Patients were randomized 3:1 to receive either a 25 mg subcutaneous injection of vutrisiran once every three months or 0.3 mg/kg intravenous infusion of patisiran once every three weeks as a reference comparator for 18 months. The primary endpoint is the mean change from baseline in the modified Neuropathy Impairment Score +7, or mNIS+7, at nine months as compared to the external placebo control arm of the previously completed APOLLO Phase 3 study of patisiran, upon which the approval of ONPATTRO was based. The two secondary endpoints at nine months are changes in quality of life assessed by the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy, or Norfolk QoL-DN, score and gait speed assessed by the time 10-meter walk test, both compared to historical placebo. Changes from baseline in NT-proBNP were evaluated as an exploratory endpoint at nine months. Additional secondary and exploratory endpoints will be evaluated at 18 months. In January 2021, we reported positive topline results from HELIOS-A.

- *Efficacy and Safety Results:* At nine months, vutrisiran met the primary endpoint (p less than 0.001) and achieved statistically significant results (p less than 0.001) for each of the Norfolk QoL-DN and 10-meter walk test secondary endpoints. In addition, a majority of patients showed reversal of polyneuropathy manifestations of disease with

improvements in neuropathy impairment and QoL, relative to baseline. Vutrisiran treatment also showed improvement compared to placebo on the exploratory cardiac biomarker endpoint, NT-proBNP (nominal p less than 0.05). Vutrisiran also demonstrated an encouraging safety and tolerability profile. There were two study discontinuations (1.6 percent) due to adverse events in the vutrisiran arm by month nine, both due to deaths, neither of which were considered related to study drug. There were two serious adverse events, or SAEs, deemed related to vutrisiran by the study investigator, consisting of dyslipidemia and urinary tract infection. Treatment emergent adverse events, or AEs, occurring in 10 percent or more patients included diarrhea, pain in extremity, fall and urinary tract infections, with each of these events occurring at a similar or lower rate as compared with historical placebo. Injection site reactions were reported in five patients (4.1 percent) and were all mild and transient. There were no clinically significant changes in liver function tests.

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 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 events. 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.

Our Other Marketed Products

GIVLAARI (givosiran) — Acute Hepatic Porphyria (AHP)

GIVLAARI (givosiran) is our second approved RNAi therapeutic and the world's first-ever GalNAc-conjugate RNA therapeutic to be approved. GIVLAARI works by specifically reducing induced liver aminolevulinic acid synthase 1 mRNA, leading to reduction of toxins associated with attacks and other disease manifestations of AHP. In the U.S., GIVLAARI (givosiran) injection for subcutaneous use is approved for the treatment of adults with AHP. GIVLAARI was reviewed by the FDA under Priority Review and had previously been granted Breakthrough Therapy and Orphan Drug Designations in the U.S. In March 2020, the EC granted marketing authorization in the EU for GIVLAARI for the treatment of AHP in adults and adolescents aged 12 years and older. GIVLAARI was reviewed under accelerated assessment by the EMA and had previously been granted PRIME and Orphan Drug Designations in the EU. We received additional marketing authorizations for GIVLAARI for the treatment of AHP in adults in Brazil in July 2020 and in Canada in October 2020. We have also filed for regulatory approval for givosiran (the non-branded drug name for GIVLAARI) in Switzerland, Israel, and Japan and additional regulatory filings are pending or planned in 2021 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 liver disease including hepatocellular carcinoma.

In August 2019, 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. Under the agreement, Ironwood's clinical sales specialists promote GIVLAARI in the U.S. to the gastroenterologists and other HCPs that it already calls on for its own marketed product. In December 2020, we amended the U.S. GI disease education and promotional agreement with Ironwood to revise the financial structure and the minimum performance requirements, and Ironwood's commercial field personnel continue to provide AHP disease education and promote GIVLAARI to gastroenterologists and other HCPs.

OXLUMO (lumasiran)— Primary Hyperoxaluria Type 1 (PH1)

Our third approved RNAi therapeutic, OXLUMO, is an RNAi therapeutic targeting hydroxyacid oxidase 1, or HAO1, for the treatment of PH1. HAO1 encodes glycolate oxidase, or GO, an enzyme upstream of the disease-causing defect in PH1. OXLUMO works by degrading HAO1 mRNA and reducing the synthesis of GO, which inhibits hepatic production of oxalate, the toxic metabolite responsible for the clinical manifestations of PH1. OXLUMO utilizes our ESC-GalNAc-conjugate technology, which enables subcutaneous dosing with increased potency and durability and a wide therapeutic index. In

November 2020, the EC granted marketing authorization for OXLUMO (lumasiran) for the treatment of PH1 in all age groups, following a positive Committee for Medicinal Products for Human Use, or CHMP, opinion. OXLUMO was previously granted an Accelerated Assessment and a PRIME Designation by the EMA and an Orphan Designation in the EU. Also, in November 2020, OXLUMO (lumasiran) subcutaneous injection was approved by the FDA for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients. OXLUMO was reviewed by the FDA under Priority Review and had previously been granted Breakthrough Therapy, Orphan Drug, and Rare Pediatric Disease Designations. With the approval of OXLUMO, the FDA has granted us a pediatric rare disease priority review voucher that entitles us to designate a single new drug application to qualify for a priority review in the future.

PH1 is an ultra-orphan genetic disease that affects an estimated one to three individuals per million in the U.S. and Europe. PH1 is characterized by oxalate overproduction in the liver. The excess oxalate 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 (calcification of the kidneys). PH1 is associated with a progressive decline in kidney function, which exacerbates the disease as the excess oxalate can no longer be effectively excreted, resulting in subsequent accumulation and deposition of oxalate in bones, eyes, skin, and heart, leading to severe illness and death. Management options prior to availability of OXLUMO were limited to hyperhydration, crystallization inhibitors and, in a minority of patients with a specific genotype, pyridoxine (vitamin B6). These measures do not adequately address oxalate overproduction but instead help to delay inevitable progression to kidney failure and the need for intensive dialysis as a bridge to a dual or sequential liver/kidney transplant. Liver transplantation is the only intervention that addresses the underlying metabolic defect, but is associated with high morbidity and mortality, and life-long immunosuppression. Prior to the approval of OXLUMO, there were no approved pharmaceutical therapies for PH1.

The regulatory approvals of OXLUMO in the U.S. and EU were based on positive results from both the ILLUMINATE-A and ILLUMINATE-B Phase 3 pivotal studies of lumasiran in patients with PH1. We are also conducting ILLUMINATE-C – a global Phase 3 study of lumasiran in PH1 patients of all ages with advanced renal disease, with topline results expected in mid-2021.

ILLUMINATE-C

- ILLUMINATE-C is an ongoing single-arm, open-label, multinational Phase 3 study to evaluate the safety and efficacy of lumasiran in PH1 patients of all ages and advanced renal disease (eGFR $\leq$ 45 mL/min/1.73m^2 or elevated serum creatinine for patients <12 months of age). In December 2020, we completed enrollment in this study. Cohort A enrolled six patients with advanced PH1 who do not yet require dialysis and Cohort B enrolled 15 patients who are dialysis-dependent. The dosing regimen is based on weight with three monthly starting doses followed by ongoing monthly or quarterly doses. The primary endpoint of the study is the percent change in plasma oxalate from baseline to month six. Key secondary endpoints are designed to evaluate additional measures of plasma oxalate and changes in urinary oxalate, and quality of life assessments. Renal function, frequency and mode of dialysis, frequency of renal stone events, and measures of systemic oxalosis will also be evaluated in the extension period of the study.
- In addition to our ILLUMINATE program, we intend to evaluate the safety and efficacy of lumasiran in patients with recurrent kidney stones in a Phase 2 study planned to initiate in late 2021.

Leqvio (inclisiran) — Hypercholesterolemia

Leqvio, our fourth approved RNAi therapeutic, developed and commercialized by our partner, Novartis, is the first and only siRNA therapy (or RNAi therapeutic) for the treatment of adults with hypercholesterolemia or mixed dyslipidemia, and is the first RNAi therapeutic approved for a common disease. Leqvio is a subcutaneously administered RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, to reduce low-density lipoprotein cholesterol, or LDL-C, levels via an RNAi mechanism of action and could help improve outcomes for patients with ASCVD, a deadly form of cardiovascular disease. Based on the results of the ORION clinical development program, in December 2020, following a positive CHMP opinion, the EC granted marketing authorization for Leqvio (inclisiran) for the treatment of adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximally tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. In December 2020, the FDA issued a complete response letter regarding Novartis' NDA for inclisiran, stating that the agency could not approve the NDA by the Prescription Drug User Fee Act, or PDUFA, action date due to unresolved facility inspection-related conditions. Novartis is working closely with the third-party manufacturer and the FDA to obtain approval as soon as possible, and has guided for a resubmission of its NDA in Q2-Q3 2021. 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 (acquired by Novartis in January 2020) 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. Following its acquisition of MDCO, Novartis has all of the rights and obligations under the MDCO agreement. A description of the MDCO agreement is included below under the heading "Strategic Alliances and Collaborations."

Regulatory filings for inclisiran were based on positive results from the robust ORION clinical development program that included a comprehensive set of clinical trials to assess LDL-C lowering and safety in over 3,600 patients.

Additional Late-Stage Clinical Development Programs

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. In October 2020, Sanofi Genzyme announced that it voluntarily paused dosing in all ongoing fitusiran clinical studies to assess reports of non-fatal thrombotic events in patients participating in the ATLAS Phase 3 program. Following an assessment of available data and alignment with the FDA, in December 2020, Sanofi Genzyme announced that it would resume fitusiran dosing in ongoing adolescent and adult clinical studies. Sanofi Genzyme has since resumed fitusiran dosing in ongoing adolescent and adult studies in certain countries with protocol amendments to address adjustments to dose and dosing regimen. To allow for the appropriate collection and assessment of safety and efficacy data under the amended protocols, Sanofi Genzyme expects that global regulatory submission timelines for the adult and adolescent studies will be delayed, subject to alignment with health authorities. Fitusiran has received both U.S. and EU Orphan Drug Designations for the treatment of hemophilia A and B.

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 and Collaborations."

Early-Stage Clinical Development Programs

Cemdisiran — Complement-Mediated Diseases

Cemdisiran is a subcutaneously administered, investigational RNAi therapeutic targeting the C5 component of the complement pathway in development for the treatment of complement-mediated diseases. The complement system plays a central role in immunity as a protective mechanism for host defense, but its dysregulation results in life-threatening complications in a broad range of human diseases including paroxysmal nocturnal hemoglobinuria, amongst others.

Cemdisiran is currently being advanced by us as a monotherapy, and enrollment in our Phase 2 clinical trial of cemdisiran in patients with IgA nephropathy is ongoing. Cemdisiran is also being evaluated by our partner, Regeneron, in combination with Regeneron's pozelimab (REGN3918), an anti-C5 monoclonal antibody, in a Phase 1 study in normal healthy volunteers and patients with paroxysmal nocturnal hemoglobinuria.

ALN-AGT — Hypertension

ALN-AGT is a subcutaneously administered, investigational RNAi therapeutic targeting liver-expressed angiotensinogen for the treatment of hypertension in high unmet need populations. Hypertension is a complex multifactorial disease clinically defined as a systolic blood pressure of above 130 mm Hg or a diastolic blood pressure of greater than 80 mm Hg. Approximately 47 percent of U.S. adults live with hypertension with more than half of patients on medication remaining above the blood pressure target level. Despite the availability of antihypertensive medications, there remains an unmet medical need, particularly given the poor rates of adherence to existing therapies and peak and trough effects. In particular, there are a number of high unmet need settings where novel approaches to hypertension are warranted, including resistant and refractory hypertension, chronic kidney disease, and heart failure.

In November 2020, we reported positive interim data from the ongoing Phase 1 study of ALN-AGT, and we expect to initiate the KARDIA-1 and -2 Phase 2 studies of ALN-AGT in mid-2021.

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

ALN-HBV02 (VIR-2218) is a subcutaneously administered, investigational RNAi therapeutic targeting the HBV genome for the treatment of chronic HBV infection, which is being advanced by our collaborators at Vir. ALN-HBV02 is designed to inhibit expression of all HBV proteins, including hepatitis B surface antigen. Almost one-third of the world's population have previous or current HBV infection. Worldwide, more than 250 million people are chronically infected with HBV, and an estimated 1 million people die each year from complications of chronic HBV such as cirrhosis and hepatocellular carcinoma. Current treatment options include life-long suppressive antiviral therapies. There is a significant need for safe and convenient novel therapeutics that restore the host immune response, leading to control of the virus after a finite duration of therapy, which is the definition of a functional cure.

The safety and efficacy of VIR-2218 are currently being investigated in an ongoing Phase 2 trial. In addition, Vir initiated a Phase 2 combination trial of VIR-2218 with pegylated interferon-alpha, with initial clinical data anticipated in 2021.

ALN-HSD – Non-alcoholic Steatohepatitis

ALN-HSD is a subcutaneously administered, investigational RNAi therapeutic targeting HSD17B13 in development in collaboration with our partner, Regeneron, for the treatment of NASH. NASH is a highly prevalent chronic liver disease characterized by the accumulation fat within hepatocytes, hepatocyte injury, and hepatic inflammation, which can lead to progressive fibrosis, cirrhosis, and hepatocellular carcinoma. Comorbidities include obesity, metabolic syndrome, and type 2 diabetes. Approximately 16 million people in the U.S. live with NASH, with prevalence of the disease increasing due to rising rates of obesity. NASH is projected to be the leading indication for liver transplants in developed countries within the next several years. There are currently no approved medical therapies for NASH.

In November 2020, we announced that we had initiated dosing in a Phase 1 study to evaluate the safety and preliminary pharmacodynamic activity of ALN-HSD in healthy volunteers and patients with NASH.

Additional Early-Stage and Pre-clinical Programs

In addition to the programs listed above, we are also advancing other earlier-stage pipeline programs and plan to file four or more investigational new drug applications, or INDs, or CTAs from our organic product engine per year by the end of 2025. We also intend to continue to build on our progress with extra-hepatic delivery during 2021, advancing our eye and CNS programs under our collaboration with Regeneron, as well as continuing to advance lung delivery of RNAi therapeutics in connection with our SARS-COV-2 genome collaboration with our partners at Vir.

Our Collaboration and Licensing Strategy

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

Our collaboration strategy is to form alliances that create significant value for ourselves and our collaborators in the advancement of RNAi therapeutics as a new class of innovative medicines. Specifically, with respect to our 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. In July 2020, Regeneron exercised its co-development/co-commercialization option on our first CNS-targeted development candidate, ALN-APP, an investigational RNAi therapeutic in development for the treatment of hereditary cerebral amyloid angiopathy and autosomal dominant Alzheimer's Disease, which we are leading.

With respect to our Cardio-Metabolic pipeline, in March 2013, we entered into an exclusive, worldwide license with MDCO (acquired by Novartis in January 2020) 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 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 April 2020, we entered into a development and commercialization collaboration with Dicerna to advance investigational RNAi therapeutics for the treatment of alpha-1 liver disease.

With respect to our Hepatic Infectious Disease pipeline, in October 2017, we announced an exclusive licensing agreement with Vir for the development and commercialization of RNAi therapeutics for infectious diseases, including chronic HBV infection. In March 2020, we announced an expansion of our exclusive licensing agreement with Vir to include the development and commercialization of RNAi therapeutics targeting SARS-CoV-2, the virus that causes the disease COVID-19. In April 2020, we further expanded our broad multi-target existing collaboration for the development and commercialization of RNAi therapeutics for infectious diseases to include up to three additional targets focused on host factors for SARS-CoV-2, including angiotensin converting enzyme-2, or ACE2, and transmembrane protease, serine 2, or TMPRSS2.

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 and Collaborations

We have formed, and intend to continue to form, strategic alliances and collaborations to gain access to the financial, technical, clinical and commercial resources necessary to develop and market RNAi therapeutics. We expect these alliances and collaborations to provide us with financial support in the form of upfront cash payments, license fees, equity investments, research, development, and sales and marketing support and/or funding, milestone payments and/or royalties or profit sharing based on sales of RNAi therapeutics. Below is a brief description of our key strategic alliances, financial collaboration 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 2 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. In July 2020, Regeneron exercised its co-development/co-commercialization option on our first CNS-targeted development candidate, ALN-APP, an investigational RNAi therapeutic in development for the treatment of hereditary cerebral amyloid angiopathy and autosomal dominant Alzheimer's Disease, which we are leading.

For more information regarding the Regeneron Collaboration, including the ongoing or expected financial and accounting impact on our business, please read Note 4, Net Revenues from Collaborations, 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, Net Revenues from Collaborations, to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this annual report on Form 10-K.

Novartis AG. 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. In January 2020, MDCO was acquired by Novartis and in December 2020, the EC granted marketing authorization for Leqvio (inclisiran) for the treatment of adults with hypercholesterolemia or mixed dyslipidemia, following a positive CHMP opinion. Inclisiran remains under regulatory review in the U.S. In December 2020, the FDA issued a complete response letter regarding Novartis' NDA for inclisiran, stating that the agency could not approve the NDA by the PDUFA action date due to unresolved facility inspection-related conditions. For more information regarding the MDCO agreement, including its ongoing financial and accounting impact on our business, please read Note 4, Net Revenues from Collaborations, 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. In March and April 2020, we entered into amendments to the Vir agreement to expand our collaboration to include the development and commercialization of RNAi therapeutics targeting SARS-CoV-2, the virus that causes the disease COVID-19, along with three additional targets focused on human host factors for SARS-CoV-2, including ACE2 and TMPRSS2 and potentially a third mutually selected host factor target. We further amended the Vir Agreement in December 2020, such that we are solely responsible for conducting pre-clinical research activities under the pre-clinical development plan at our discretion and sole expense and effective as of July 1,

2020, we are responsible for all pre-clinical development costs incurred under such plan. For more information regarding the Vir agreement, including its ongoing financial and accounting impact on our business, please read Note 4, Net Revenues from Collaborations, to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this annual report on Form 10-K.

Strategic Financing Collaboration

The Blackstone Group Inc. In April 2020, we entered into a strategic financing collaboration with certain affiliates of Blackstone to accelerate our advancement of RNAi therapeutics. In connection with the collaboration, Blackstone will provide us up to $2.0 billion in financing, including $1.0 billion in committed payments to acquire 50% of royalties and 75% of commercial milestones payable to us in connection with sales of Leqvio, up to $750.0 million in a first lien senior secured term loan, and up to $150.0 million towards the development of vutrisiran and ALN-AGT pursuant to the funding agreement finalized in August 2020. As part of the strategic financing collaboration, Blackstone also purchased an aggregate of $100.0 million of our common stock. Please read Note 5 and Note 8 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 additional details on our transaction with Blackstone.

Other Strategic License Agreements

Dicerna Pharmaceuticals, Inc. In April 2020, we and Dicerna formed a development and commercialization collaboration on investigational RNAi therapeutics for the treatment of alpha-1 liver disease. Under the development and commercialization agreement entered into between the parties, our ALN-AAT02 and Dicerna's DCR-A1AT, investigational RNAi therapeutics, each in Phase 1/2 development, will be explored for the treatment of alpha-1 liver disease. In addition, in April 2020, we and Dicerna entered into a Patent Cross-License Agreement, pursuant to which each party agreed to cross-license its respective intellectual property related to our lumasiran program and Dicerna's nedosiran program, each for the treatment of PH.

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. 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. 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 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, in exchange for option fees, and future milestone and royalty payments from Ionis for RNAi programs that incorporate certain of our intellectual property, 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.

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 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 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 NCE exclusivity until November 20, 2024, and ODE until November 20, 2026. In connection with our EMA approval on March 2, 2020, the EMA granted GIVLAARI Marketing Exclusivity and ODE until March 2, 2030.

OXLUMO

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
9828606	United States	Compositions of Matter	12/26/2034	Dicerna Pharmaceuticals
10131907	United States	Compositions of Matter & Methods of Use	8/24/2028	Alnylam
10435692	United States	Methods of Use	12/26/2034	Dicerna Pharmaceuticals
10465195	United States	Compositions of Matter & Methods of Use	12/26/2034	Dicerna Pharmaceuticals
10478500	United States	Compositions of Matter & Methods of Use	10/9/2035	Alnylam
10487330	United States	Compositions of Matter & Methods of Use	12/26/2034	Dicerna Pharmaceuticals
10612024	United States	Compositions of Matter	8/14/2035	Alnylam
10612027	United States	Compositions of Matter & Methods of Use	8/14/2035	Alnylam
3087184	Europe	Compositions of Matter	12/26/2034	Dicerna 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 23, 2020, the FDA granted OXLUMO NCE exclusivity until November 23, 2025. In connection with our EMA approval on November 19, 2020, the EMA granted OXLUMO Marketing Exclusivity and ODE until November 19, 2030.

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, GIVLAARI® and the GIVLAARI logo with registration pending for OXLUMO™ and the OXLUMO logo.

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.

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 some 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, F. Hoffmann-La Roche Ltd, or Roche, Silence Therapeutics plc, or Silence, and its collaborators, AstraZeneca plc, or AstraZeneca, and Mallinckrodt plc, Arbutus Biopharma Corp., or Arbutus, Sylentis, S.A.U., or Sylentis, Dicerna, and its collaborators, Boehringer Ingelheim, Novo Nordisk A/S, Alexion Pharmaceuticals, Inc. and Eli Lilly and Company, WAVE Life Sciences Ltd., or WAVE, Silenseed Ltd., Ascletis Pharma Inc., Biomics Biopharma, Avidity Biosciences Inc., Dyne Therapeutics Inc., or Dyne, Atalanta Therapeutics Inc., 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., MiNA Therapeutics, 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 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. (acquired by Ionis in October 2020), or Akcea, Antisense Therapeutics, Ltd., Dyne, 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 many countries) 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., EU and Japan; (indication varies by region)	Daily oral capsule
TEGSEDI (inotersen)	Ionis	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)
IONIS-TTR-L_{Rx}	Ionis	ASO to reduce production of TTR Protein	Phase 3	Monthly SC
Acoramidis (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)	Small molecule repurposed generic drug	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	Phase 1	Intravenous (IV)

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 is approved in the U.S. for the treatment of adults with AHP, and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older, 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. In addition to OXLUMO, which was recently approved in the U.S. for the treatment of primary hyperoxaluria, or PH, type 1, and in the EU for the treatment of PH type 1 in patients of all ages, currently used treatments for PH include hyper hydration, oral citrate or dual liver/kidney transplantation. Transplantation is costly and is an invasive procedure, which carries significant morbidity and mortality. This leaves a high unmet medical need for a severe and primarily pediatric disorder. Presently, there are several investigational drugs in varying stages of clinical development for the treatment of PH. We believe that the following drug candidates, if approved, could compete with OXLUMO:

Drug	Company	Drug Description	Phase	Administration/Dosing
Nedosiran	Dicerna	siRNA to reduce production of LDHA enzyme	Phase 2 (pivotal)	SC with monthly dosing expected
Oxabact OC5	OxThera AB	Anaerobic bacteria that metabolize oxalate in the gut	Phase 3	Twice daily oral dose
Reloxaliase	Allena Pharmaceuticals, Inc.	Oxalate-degrading enzyme for enteric hyperoxaluria	Phase 3 (for enteric hyperoxaluria)	Up to five daily oral doses

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

Hypercholesterolemia. In addition to Leqvio, which was approved in the EU in December 2020 for the treatment of adults with hypercholesterolemia or mixed dyslipidemia, 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 Leqvio:

Drug	Company	Drug Description	Phase	Administration/Dosing
Repatha	Amgen	Anti-PSCK9 mAb	Approved	SC
Praluent	Sanofi Genzyme	Anti-PSCK9 mAb	Approved	SC
Vascepa	Amarin Corporation	Omega-3 lipid proven to reduce LDL-C and CV Risk	Approved	Oral
NEXLETOL (Bempedoic Acid)	Esperion Therapeutics, Inc.	Oral fatty acid and cholesterol synthesis dual inhibitor	Approved	Oral
REGN1500 (evinacumab)	Regeneron	Anti-ANGPTL3 mAb for hypercholesterolemia	Phase 3 in HoFH	SC
Arrowhead-ARO-ANG3	Arrowhead	siRNA targeting ANGPTL3	Phase 1/2	SC
Vupanorsen	Akcea / Pfizer	ASO therapy to reduce levels of ANGPTL3	Phase 2b	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
HEMLIBRA (Roche)	Bispecific antibody mimetic of FVIII	Approved	SC - Monthly
Marstacimab (Pfizer)	Anti-TFPI antibody	Phase 3	SC - Weekly
RG6357 (Roche)	Gene therapy	Phase 3	IV – Single Administration
Hemophilia B			
Rixubis (Takeda), Rebinyn (Novo Nordisk), BeneFIX (Pfizer), Alprolix (Bioverativ), Idelvion (CSL Behring)	Recombinant FIX factor products	Approved	IV
Etranacogene dezaparvovec (uniQure/CSL Behring)	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
Marstacimab (Pfizer)	Anti-TFPI antibody	Phase 3	SC - Weekly
Hemophilia A and B			
Concizumab, anti-TFPI (Novo Nordisk)	Anti-TFPI antibody	Phase 2	SC
Marstacimab (Pfizer)	Anti-TFPI antibody	Phase 3	SC - Weekly

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 drug candidates, 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 including FDA's good laboratory practice requirements. The results of nonclinical testing are submitted to the FDA as part of an IND, together with chemistry, manufacturing and controls, or CMC, information, analytical and stability data, a proposed clinical trial protocol and other information. Clinical testing in humans may not commence until an IND is in effect.

An IND becomes effective 30 days after receipt by the FDA unless the FDA notifies the sponsor that the proposed investigation(s) are subject to a clinical hold. If the FDA imposes a clinical hold, the FDA's concerns must be resolved prior to the commencement of clinical trials. The IND review process can result in substantial delay and expense. We, an IRB, or the FDA may, at any time, suspend, terminate, significantly modify, restrict 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.

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 for 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 participating in the study. An IRB or a clinical trial sponsor also may modify, 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 clinical 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 PDUFA, as amended, each NDA must be accompanied by an application fee. For fiscal year 2021, the application fee for each NDA requiring clinical data is approximately $2.9 million. PDUFA also imposes an annual program fee for each approved prescription drug, which has been set at approximately $336,000 for fiscal year 2021. 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 NDA 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 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 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 for a narrower patient population 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, AE reporting, submission of other periodic reports, field alerts, 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 in the approved application. 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 or cannot be completed due to COVID-19 related restrictions, the FDA may defer action on an application or 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. In some instances, 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 based on the intended use and technological characteristics) 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 and 505(b)(2) 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 following the approval of the listed drug 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 affects more than 200,000 individuals and 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 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 previously approved drug. 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. To demonstrate a drug is “clinically superior” to the previously approved orphan drug, a sponsor must show that the drug provides a significant therapeutic advantage over and above the previously already approved drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care.

A designated orphan drug may not receive Orphan Drug Exclusivity for a use that is broader than the indication for which it received Orphan Drug Designation and regulatory approval. 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, or if the manufacturer chooses to provide consent to approval of other applications.

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 to the extent that the indication being sought under the marketing application is within the scope of the designated orphan use. 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 initial 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 because many of the features of Fast Track designation will not apply after that time. 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, and has also granted Fast Track designation to vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis.

Any drug or biological product that receives a Fast Track designation, 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 receipt, instead of ten months from the date of receipt, 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 and ideally before initiation of the pivotal clinical trial intended to serve as the primary basis for demonstration of efficacy to obtain the full benefits of the designation. 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, approved in November 2020. We intend to request breakthrough therapy designation for our other product candidates, if applicable.

Rare Pediatric Disease Designation and Priority Review Voucher

In addition, the FDCA provides a rare pediatric disease priority review voucher, or PRV, program. The program is intended to incentivize the development of new drug and biological products for the prevention and treatment of "rare pediatric diseases," that is, any disease that is a rare disease and is serious or life-threatening with the serious or life-threatening manifestations primarily affecting individuals from birth to 18. Under this program, the sponsor of an application for a rare pediatric disease drug may be eligible to obtain a voucher that can be used to obtain a priority review for a subsequent human drug application. The FDA recommends that a sponsor request rare pediatric disease designation before submission of the rare pediatric disease product application. The rare pediatric disease designation does not guarantee that the sponsor will receive a PRV. The FDA will award a PRV upon approval of the marketing application if the sponsor requests such a voucher in their marketing application and if the application meets the eligibility criteria. If awarded, the PRV may be transferred unlimited times. The rare pediatric disease PRV program was initially created in 2012, and Congress has extended the PRV program through September 30, 2024, with the potential for PRVs to be granted through September 30, 2026. The FDA awarded a rare pediatric disease PRV to us upon approval of the NDA for lumasiran in November 2020.

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. Future legislation could limit payments for pharmaceuticals such as the drug candidates that we are developing. Likewise, the Biden administration has indicated that lowering prescription drug prices is a priority, but we do not yet know what steps the administration will take or whether such steps will be successful.

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 care-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. Violation of the FCPA could result in substantial civil and criminal penalties and remedies, including fines, disgorgement, and imprisonment.

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 not expected to come into application before December 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 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 no earlier than December 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 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 2020, we filed for regulatory approval for our commercial products in a number of jurisdictions worldwide, and regulatory filings in additional countries are planned for ONPATTRO, GIVLAARI and OXLUMO in 2021, and we will have to follow the specific regulations in such jurisdictions and such other countries in which we file, 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 marketing applications 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 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, drug product 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, GIVLAARI and OXLUMO, 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, and we have entered into manufacturing services agreements with Agilent for such supply of ONPATTRO and 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.

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. In addition, during 2020, we completed construction and qualification of our cGMP manufacturing facility in Norton, Massachusetts where we will manufacture drug substance for clinical and, eventually, commercial use. In December 2020, we began cGMP operations, and we believe this facility will enable us to initiate manufacturing for 10-15 new early-stage programs over the next few years, as well as provide us the manufacturing capabilities to support our late-stage and commercial programs in the future.

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 our new manufacturing facility, 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. Over the last several years, 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 four 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 and OXLUMO, we have global rights to develop and commercialize;
- For Leqvio, we have granted MDCO, which was acquired by Novartis 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, GIVLAARI and OXLUMO, 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, OXLUMO 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, as part of our planned transition to a top 5 biotech in market capitalization by the end of 2025 and consistent with our *Alnylam P^5x25* strategy, we are now advancing RNAi therapeutics beyond rare diseases into prevalent disease opportunities. With the recent approval of Leqvio, the first RNAi therapeutic approved for a common disease, we believe the RNAi therapeutic profile supports the expansion to prevalent diseases, including addressing many unmet needs in common disease settings such as hypertension, NASH, gout and diabetes.

In addition, with respect to GIVLAARI, in August 2019, 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. Under the agreement, Ironwood's clinical sales specialists promote GIVLAARI in the U.S. to the gastroenterologists and other HCPs that it already calls on for its own marketed product. In December 2020, we amended the U.S. GI disease education and promotional agreement with Ironwood to revise the financial structure and the minimum performance requirements, and Ironwood's commercial field personnel continue to provide AHP disease education and promote GIVLAARI to gastroenterologists and other HCPs. 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. As of the beginning of 2021, we have completed at least 30 VBAs with multiple commercial payers, including 19 for ONPATTRO, 10 for GIVLAARI, and one for OXLUMO. In our VBAs for GIVLAARI we introduced an ultra-rare disease Prevalence Based Adjustment that lowers the price of the medicine if the number of patients identified within a plan population exceeds the expected disease prevalence. For OXLUMO, we have established a new VBA component called a Patient Need Adjustment that provides payers with greater budget certainty for medicines administered across a broad range of patient age groups. Discussions with payers continue for our marketed products. Outside of the U.S. we believe we have made strong progress in terms of patient access and have established availability of ONPATTRO in more than 20 countries through direct reimbursement or expanded access.

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, assuming regulatory approval. With respect to commercially approved products, throughout 2020, we continued to build our commercial capabilities, 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 and GIVLAARI to also support the launch of OXLUMO, as well as the potential launch of vutrisiran, assuming 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 launches of ONPATTRO and GIVLAARI.

Human Capital Management

As of December 31, 2020, we employed 1,453 full-time employees, of whom approximately 1,147 were employed in the U.S. and approximately 306 were employed outside of the U.S. None of our employees in the U.S. are represented by a labor union or covered by collective bargaining agreements, and we believe our relationship with our employees is good. During 2020, we enhanced our capabilities by adding 130 new full-time employees. The new employees were hired to support a variety of functions and key initiatives, including extending our research, clinical and pre-clinical pipeline development, as well as our medical affairs, manufacturing and commercialization capabilities, with hires in commercial, clinical development and operations, research, medical affairs, manufacturing, and general and administrative functions. We expect to continue to add additional employees in 2021, with a focus on further enhancing our capabilities and increasing our capacities in these areas, as well as expanding our geographic reach as we continue the global launches of our approved medicines and prepare for the planned launch of vutrisiran, assuming regulatory approval.

We consider the intellectual capital, skills and experience of our employees to be an essential driver of our business and key to our future prospects. We face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, and we believe that our future success will depend in large part on our continued ability to attract and retain highly skilled employees. To attract qualified applicants to our company and retain our employees, we offer a total rewards package consisting of base salary and cash target bonus targeting the 50th to 65th percentile of market based on geography, a comprehensive benefit package and equity compensation for every employee. Annual cash bonus opportunity and equity compensation increase as a percentage of total compensation based on level of responsibility. Any actual bonus payout is based solely on our performance against our corporate goals in the case of executive officers and is based on a combination of individual performance and corporate performance (or regional or national commercial performance metrics, as applicable) in the case of all other employees.

As a global commercial-stage biopharmaceutical company, we believe that our long-term success and ability to deliver innovative, safe and effective medicines to patients requires a diverse and inclusive workforce. We value diversity at all levels of the organization and continue to focus on extending our diversity, equity and inclusion initiatives across our entire workforce, from: working with managers to develop strategies for building diverse, high performing teams; to ensuring that we attract, develop and retain diverse talent from all backgrounds; to increasing awareness within our company of unconscious biases, and supporting affinity groups comprised of individuals who are underrepresented in our company, industry or society, such as women, members of the LGBTQ community and people of color. In addition, we pride ourselves on an open culture that respects co-workers, values employees' health and well-being and fosters professional development. We support employee growth and development in a variety of ways including with group training, individual mentoring and coaching, conference attendance and tuition reimbursement. Our management conducts annual employee engagement surveys and reports to our board of directors on human capital management topics, including corporate culture, diversity, equity and inclusion, employee development and retention, and compensation and benefits. Similarly, our board of directors regularly provides input on important decisions relating to these matters, including with respect to employee compensation and benefits, talent retention and development.

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, people, culture and 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

We operate in an environment that involves a number of significant risks and uncertainties. We caution you to read the following risk factors, which have affected, and/or in the future could affect, our business, prospects, operating results, and financial condition. The risks described below include forward-looking statements, and actual events and our actual results may differ materially from these forward-looking statements. Additional risks and uncertainties not currently known to us or that we currently deem immaterial may also impair our business, prospects, operating results, and financial condition. Furthermore, additional risks and uncertainties are described under other captions in this report and should also be considered by our investors.

Risks Related to Our Business

Risks Related to Our Financial Results

The current pandemic of COVID-19 and the future outbreak of other highly infectious or contagious diseases, could have a material adverse impact on our business, financial condition and results of operations, including our commercial operations and sales, clinical trials and pre-clinical studies.

In December 2019, a novel strain of coronavirus, or COVID-19, was reported to have surfaced and it has since reached multiple regions, countries and cities, including Cambridge, Massachusetts where our primary office and laboratory space is located, and all countries in which we have offices. The COVID-19 pandemic continues to evolve and the ultimate impact of this pandemic is highly uncertain and subject to change. To date, the pandemic has led to the implementation of various responses, including government-imposed quarantines, travel restrictions and other public health safety measures. Certain jurisdictions have begun re-opening only to return to restrictions in the face of increases in new COVID-19 cases. COVID-19 has and will likely continue to impact our operations and those of our third-party partners and the ultimate impact on our business and financial results remains uncertain and cannot be predicted with confidence, and will depend on many factors, including the scope, severity, duration and any recurrence of the COVID-19 pandemic, including through any new variant strains of the underlying virus, the actions taken to contain the pandemic or mitigate its impact, the direct and indirect economic effects of the pandemic and containment measures, and the availability and efficacy of vaccines and treatments for COVID-19, among others. The continued development and fluidity of the COVID-19 pandemic precludes any prediction as to its full impact on our business. Nevertheless, the COVID-19 pandemic may adversely affect our business, financial condition and results of operations.

In response to the spread of COVID-19, we took, and have continued to take, temporary precautionary measures intended to help minimize the risk of the virus to our employees and their families, including implementing a global work from home policy for nearly all employees who are able to perform their duties remotely, and have generally restricted on-site staff to only those personnel and contractors who perform activities that need to be completed on-site, limited the number of staff in any given laboratory, manufacturing facility or other facility and implemented safety practices and procedures for those individuals who are required to work in our facilities, including but not limited to mandatory health screening, the use of face coverings, physical distancing requirements and increased cleaning protocols, as well as voluntary onsite testing. We also suspended non-essential business travel for our employees and may take further measures as the pandemic continues. In addition, our customer-facing employees in most markets moved and could again need to move to virtual interactions with healthcare providers, administrators, patients, payers, regulators and other government employees. We expect to adopt and implement additional precautions commensurate with any expansion of employees returning to physical locations, and at this time, we cannot predict when certain restrictions that are in place to protect our employees can be further reduced or will no longer be needed. The effects of government-imposed quarantines and our work-from-home policies may negatively impact productivity, or disrupt, delay, or otherwise adversely impact our business. Compliance with governmental measures imposed in response to COVID-19 has caused and will continue to cause us to incur additional costs, and any inability to comply with such measures can subject us to restrictions on our business activities, fines, and other penalties, any of which can adversely affect our business. In addition, the increase in certain of our employees working remotely has amplified certain risks to our business, including increased demand on our information technology resources and systems, increased phishing and other cybersecurity attacks, and any failure to effectively manage these risks, including to timely identify and appropriately respond to any cyberattacks, could adversely impact our business operations.

As a result of the COVID-19 pandemic, we may experience disruptions that could severely impact our business and operations, including our ability to successfully commercialize our approved products, ONPATTRO, GIVLAARI and OXLUMO, and due to the current pandemic, we may not be able to meet expectations with respect to commercial sales. For example, due to the impact of the COVID-19 pandemic, product revenues in the second quarter of 2020 for ONPATTRO were less than originally forecast. In addition, we may also experience decreased patient demand for our approved products if current or potential patients decide to delay treatment as a result of the COVID-19 or a future pandemic. For example, in the second quarter of 2020, we experienced a decrease in patient demand in the U.S. due to reduced adherence as some patients skipped doses or experienced dose delays while moving to new sites of care, and additionally experienced reduced requests for genetic testing through our third party genetic testing program resulting in delays in diagnoses of the rare diseases our medicines are approved to treat. In addition, business interruptions from the current or future pandemics, including staffing shortages,

production slowdowns and disruptions in delivery systems, may also adversely impact the third parties we or our partners rely on in the U.S. and abroad to sufficiently manufacture our approved products and to produce product candidates in quantities we require, which may impair our commercialization efforts, our research and development activities and the potential commercialization of our product candidates.

Additionally, timely completion of pre-clinical activities and initiation of planned clinical trials is dependent upon the availability of, for example, pre-clinical and clinical trial sites, researchers and investigators, patients or healthy volunteer subjects available for recruitment and enrollment, and regulatory agency personnel, which may be adversely affected by global health matters, such as the COVID-19 pandemic. We are conducting and plan to continue to conduct pre-clinical activities and clinical trials for our drug product candidates in geographies which have been and continue to be affected by COVID-19, and believe that the COVID-19 pandemic will have an impact on various aspects of our ongoing clinical trials and on the clinical trials and pre-clinical studies we expect to initiate in 2021. For example, certain trial sites in some of our ongoing clinical trials were restricted temporarily by the institutions where they are located from scheduling patient visits or permitting onsite monitoring due to the COVID-19 pandemic, and in some of our ongoing trials, delayed or missed doses of study drug have been reported. In addition, due to the impact of the COVID-19 pandemic, enrollment delays in our APOLLO-B Phase 3 study of patisiran for the treatment of ATTR amyloidosis with cardiomyopathy resulted in a shift in the enrollment completion date from late 2020 into early 2021. Any business interruptions caused by the COVID-19 pandemic could also delay necessary interactions with local regulators, ethics committees, manufacturing sites, research or clinical trial sites and other important agencies and contractors, which could adversely impact the clinical trials of our product candidates.

Health regulatory agencies globally may also experience disruptions in their operations as a result of the COVID-19 pandemic, which may impact review, inspection and approval timelines. Since March 2020, foreign and domestic inspections by the FDA have largely been on hold with the FDA announcing plans in July 2020 to resume prioritized domestic inspections. Should the FDA determine that an inspection is necessary for approval of a marketing application and an inspection cannot be completed during the review cycle due to restrictions on travel, the FDA has stated that it generally intends to issue a complete response letter. Further, if there is inadequate information to make a determination on the acceptability of a facility, the FDA may defer action on the application until an inspection can be completed. For example, in December 2020, the FDA issued a complete response letter regarding Novartis' NDA for inclisiran, stating that the agency could not approve the NDA by the PDUFA action date due to unresolved facility inspection-related conditions. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities.

Some factors from the COVID-19 pandemic that may delay or otherwise adversely affect enrollment in and the conduct of the clinical trials of our product candidates, as well as adversely impact our business generally, include:

- the diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, including the availability of materials necessary to conduct of our clinical trials;
- limitations on travel that could interrupt key trial activities, such as clinical trial site initiations and monitoring, domestic and international travel by employees, contractors or patients to clinical trial sites, including any government-imposed travel restrictions or quarantines that will impact the ability or willingness of patients, employees or contractors to travel to our research, manufacturing and clinical trial sites or secure visas or entry permissions, any of which could delay or adversely impact the conduct or progress of our clinical trials; and
- interruption of, or delays in receiving, supplies of our product candidates from our contract manufacturing organizations due to staffing shortages, production slowdowns or stoppages and disruptions in delivery systems.

These and other factors arising from the COVID-19 pandemic could worsen in countries that are already afflicted with COVID-19 or could return to countries where the pandemic has been partially contained, each of which could further adversely impact our ability to conduct clinical trials and our business generally, and could have a material adverse impact on our operations and financial condition and results. In addition, a recession, depression or other sustained adverse market event resulting from the COVID-19 pandemic could materially and adversely affect our business and the value of our common stock.

The ultimate impact of the COVID-19 pandemic remains highly uncertain and subject to change. We do not yet know the full extent of potential delays or impacts on our business, our commercial results, clinical trials, healthcare systems or the global economy as a whole. These effects could have a material impact on our operations, and we will continue to monitor the COVID-19 situation closely.

We are an early-stage commercial company and the marketing and sale of ONPATTRO, GIVLAARI, OXLUMO or any future products may be unsuccessful or less successful than anticipated.

In 2018, our first commercial product, ONPATTRO, was approved by the FDA and EMA, and we have since received approval and launched ONPATTRO in several additional territories. In 2019, the FDA approved our second product, GIVLAARI, which was also approved by the EMA and several other regulatory authorities, and in November 2020, the FDA and EMA approved our third product, OXLUMO. While we have commercially launched ONPATTRO, GIVLAARI and OXLUMO, we are an early-stage commercial company and there is limited information about our ability to successfully

overcome many of the risks and uncertainties encountered by companies commercializing products in the biopharmaceutical industry. We also have several product candidates in late-stage clinical development. To execute our business plan of building a profitable, top 5 biotech company, as measured by market capitalization, over the next 5 years and achieving our P^5x25 strategy and the metrics associated with such strategy, in addition to successfully marketing and selling our approved products we will need to successfully:

- execute product development activities and continue to leverage new technologies related to both RNAi and to the delivery of siRNAs to the relevant tissues and cells, including the CNS, eye and lung;
- build and maintain a strong intellectual property portfolio;
- gain regulatory acceptance for the development and commercialization of our product candidates and market success for our approved products, 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 our approved products or any future products, raise capital, if needed, repay the debt we incurred in 2020 and plan to incur in 2021, 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, 2020, we had an accumulated deficit of $4.59 billion. Although to date we have launched three products in the U.S., EU and various other countries globally, and expect to launch our commercially approved products in additional countries during 2021 and beyond, we may never attain profitability or positive cash flow from operations. For the year ended December 31, 2020, we recognized $361.5 million in net product revenues from sales of ONPATTRO, GIVLAARI and OXLUMO. While our full year 2020 operating loss improved relative to the prior year, marking 2019 as our peak operating loss year, we expect to continue to incur annual net operating losses, and will require substantial resources over the next several years as we expand our efforts to discover, develop and commercialize RNAi therapeutics, and aim to achieve sustainable non-GAAP profitability by the end of 2025. While we believe the funding provided by our strategic financing collaboration with Blackstone should enable us to achieve a self-sustainable profile without the need for future equity financing, we will depend on our ability to generate revenues to achieve this goal. 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 under our existing or new alliances.

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 build upon the success we have had 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 funds to continue our research, development and commercialization activities and if the funds we require are greater than what we have estimated, we may need to critically limit or 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 our three approved products 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, including vutrisiran, 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 operating loss year, and believe that our strategic financing collaboration with Blackstone will enable us to achieve a self-sustainable financial profile without need for future equity financing. 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:

- 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, including milestone payments related to Leqvio, which is being developed and commercialized by our partner, Novartis;
- 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 impact of COVID-19 on the initiation or completion of pre-clinical studies or clinical trials and the supply of our products or product candidates;
- 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;
- the timing, receipt and amount of sales and royalties, if any, from our approved products and our potential products, if and when approved; and
- the outcome of the regulatory review process and commercial success of drug products for which we are entitled to receive royalties, including Leqvio.

If our estimates, predictions and financial guidance relating to these factors are incorrect, we may need to modify our operating plan and may be required to seek additional funding in the future. We may do so through either collaborative arrangements, public or private equity offerings or debt financings, royalty or other monetization transactions or a combination of one or more of these funding sources. Additional funds may not be available to us on acceptable terms or at all.

In April 2020, we entered into a credit agreement, or Credit Agreement, for up to $750.0 million among us, certain of our subsidiaries (together with us, the Loan Parties), funds or accounts managed or advised by GSO Capital Partners LP (now Blackstone Alternative Credit Advisors LP) and certain other affiliates of Blackstone, and the other lenders from time to time party thereto and Wilmington Trust, National Association, as the administrative agent for the lenders. The Credit Agreement provides for a senior secured delayed draw term loan facility to be funded in three tranches, or Term Loans, each tranche to be requested by certain dates specified in the Credit Agreement, and subject to customary terms and conditions in the case of each tranche. The Term Loans mature seven years from the date of the first draw, and bear interest at a variable rate. All obligations under the Credit Agreement are secured, subject to certain exceptions, by security interests in certain assets, including the intellectual property owned by us relating to ONPATTRO, GIVLAARI and vutrisiran, the equity interests held by the Loan Parties in their subsidiaries, all of our ownership of the inclisiran royalty remaining after the royalty purchase and material real property, and certain personal property, including, without limitation, cash held in certain deposit accounts of the Loan Parties and equipment. The Credit Agreement contains negative covenants that, among other things and subject to certain exceptions, could restrict our ability to, incur additional liens, incur additional indebtedness, make investments, including acquisitions, engage in fundamental changes, sell or dispose of assets that constitute collateral, including certain intellectual property, pay dividends or make any distribution or payment on or redeem, retire or purchase any equity interests, amend, modify or waive certain material agreements or organizational documents and make payments of certain subordinated indebtedness. The Credit Agreement also requires us to have consolidated liquidity of at least $100.0 million as of the last day of each fiscal quarter. Additionally, the Credit Agreement contains certain customary representations and warranties, affirmative covenants and provisions relating to events of default. In August 2020, in connection with execution of the funding agreement for the clinical development of vutrisiran and ALN-AGT, or Funding Agreement, we entered into the First Amendment to the Credit Agreement. The First Amendment added certain intellectual property owned by us relating to ALN-AGT as collateral under the Credit Agreement, as amended, and made certain other amendments related thereto and the Funding Agreement. In December 2020, we drew down the first tranche of $200.0 million under the Credit Agreement, as amended. Our ability to satisfy our obligations under the Credit Agreement, as amended, and meet our debt service obligations will depend upon our future performance, which will be subject to financial, business and other factors affecting our operations, many of which are beyond our control. If we are unable to secure future borrowings under the term loan facility, we may not be able to replace the financing commitment on favorable terms, or at all.

The terms of any financing we may be required to pursue in the future notwithstanding the funds due or available to us from Blackstone 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. For example, pursuant to our stock purchase agreement with Blackstone, we agreed to register the resale of the shares purchased on a registration statement within 60 days of April 10, 2020, and on June 5, 2020, such registration statement was filed with the SEC. In addition, subject to certain conditions, Blackstone will be entitled to participate in registered underwritten public offerings by us if other selling stockholders are included in the registration.

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, or delay or curtail the further development of our global commercial infrastructure, 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.

Although we sold a portion of the expected royalty stream and commercial milestones from the global sales of Leqvio by our collaborator, Novartis, we are entitled to retain the remaining portion of future royalties from the global sales of Leqvio and, if certain specified thresholds are met, to the remaining portion of commercial milestone payments, and any negative developments related to Leqvio could have a material adverse effect on our receipt of those payments.

In April 2020, we sold to Blackstone 50% of the royalties payable to us with respect to net sales by Novartis, its affiliates or sublicensees of Leqvio and 75% of the commercial milestone payments payable to us under the MDCO agreement. If Blackstone does not receive royalty payments in respect of global sales of Leqvio equaling at least $1.00 billion by December 31, 2029, Blackstone's royalty interest will increase to 55% effective January 1, 2030. Our receipt of future royalty payments and a portion of commercial milestone payments may be negatively impacted if the Leqvio royalty stream and commercial milestones payments are insufficient to meet the specified thresholds. For example, in December 2020, the FDA issued a complete response letter regarding Novartis' NDA for inclisiran, stating that the agency could not approve the NDA by the PDUFA action date due to unresolved facility inspection-related conditions. While Leqvio was granted marketing authorization by the EC in Europe in December 2020, any negative impact to future royalty payments and commercial milestone payments that results from a delayed approval in the U.S. could affect our ability to meet the specified repayment thresholds. Additional factors that may have an adverse effect on the Leqvio royalty stream and commercial milestones include:

- companies working to develop new therapies or alternative formulations of products for ASCVD;
- foreign currency movement, which could have a negative impact on Novartis' sales of Leqvio, thereby reducing the royalties;
- any negative developments relating to Leqvio, such as safety, efficacy, or reimbursement issues, could reduce demand for Leqvio;
- any disputes concerning patents, proprietary rights, or license and collaboration agreements could negatively impact our receipt of commercial milestone payments or royalties; and
- adverse regulatory or legislative developments could limit or prohibit the sale of Leqvio, such as restrictions on the use of Leqvio or safety-related label changes, including enhanced risk management programs, which may significantly reduce expected royalty revenue and commercial milestone payments and could require significant expense to address the associated legal and regulatory issues.

If the revenues generated by sales of Leqvio are lower than expected, our business could be materially adversely affected.

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 impact of the COVID-19 or a future pandemic, 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. For example, due to the impact of the COVID-19 pandemic, product revenues in the second quarter of 2020 for ONPATTRO were less than originally forecast. In addition, 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 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 securities is subject to risks which may cause losses and affect the liquidity of these investments.

As of December 31, 2020, we had $1.87 billion in cash, cash equivalents and marketable securities. 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. For example, on March 27, 2020, President Trump signed into law the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, which included certain changes in tax law intended to stimulate the U.S. economy in light of the COVID-19 pandemic, including temporary changes to the treatment of net operating losses, interest deductibility limitations and payroll tax matters. 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 has the right to develop and commercialize fitusiran globally. In addition, we formed a collaboration with MDCO (which was acquired by Novartis 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, and in early 2020, we expanded our exclusive licensing agreement to include the development and commercialization of RNAi therapeutics targeting SARS-CoV-2, the virus that causes the disease COVID-19, as well as up to three human host factor targets relating to susceptibility to coronaviruses, for use in connection with the treatment, palliation, diagnosis or prevention of SARS-CoV-2 and other diseases caused by coronaviruses. In April 2020, we entered into a development and commercialization collaboration with Dicerna to advance investigational RNAi therapeutics for the treatment of alpha-1 liver disease. 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) Novartis for all future development and commercialization of Leqvio 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. For example, while Leqvio was granted marketing authorization by the EC in Europe, in December 2020, Novartis received a complete response letter from the FDA stating that the agency could not approve the NDA by the PDUFA action date due to unresolved facility inspection-related conditions, which will likely delay the launch of Leqvio in the U.S. If the revenues generated by the royalties received by Blackstone from us with respect to Leqvio sales do not reach a certain level by the end of 2029, Blackstone will be entitled to a higher royalty percentage beginning in 2030, which would have an adverse impact on our revenues beginning in 2030.

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 in certain tissues or disease areas, 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 and a subsequent pause in dosing and enrollment in fitusiran clinical studies in 2020 could contribute to further concerns about the safety of specific therapeutic candidates or therapeutic candidates for specific diseases. 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, Novartis, Vir, Dicerna 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 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. Moreover, any adverse actions by Novartis with respect to the MDCO agreement could adversely impact our ability to comply with our obligations under our agreements with Blackstone. 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, 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 products or 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 our approved products, continue to develop our current product candidates, including vutrisiran, 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, during 2020, we completed construction and qualification of our cGMP manufacturing facility in Norton, Massachusetts where we will manufacture drug substance for clinical and, eventually, commercial use. In December 2020, we began cGMP operations, and we believe this facility will enable us to initiate manufacturing for 10-15 new early-stage programs over the next few years, as well as provide us the manufacturing capabilities to support our late-stage and commercial programs in the future.

At the present time, we may manufacture limited quantities of clinical trial materials ourselves, but otherwise we continue to 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 supply of our approved products 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 manufacturing services agreements with Agilent for such supply of ONPATTRO and GIVLAARI. Similarly, we entered in to manufacturing services agreement with a separate CMO for the supply of OXLUMO. There are risks inherent in pharmaceutical manufacturing that could affect the ability of our CMOs 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. On March 27, 2020, President Trump signed into law the CARES Act in response to the COVID-19 pandemic. Throughout the COVID-19 pandemic, there has been public concern over the availability and accessibility of critical medical products, and the CARES Act enhances FDA's existing authority with respect to drug shortage measures. Under the CARES Act, manufacturers must have in place a risk management plan that identifies and evaluates the risks to the supply of approved drugs for certain serious diseases or conditions for each establishment where the drug or active pharmaceutical ingredient is manufactured. The risk management plan will be subject to FDA review during an inspection. If we experience shortages in the supply of our marketed products, our results could be materially impacted. Two vaccines for COVID-19 were granted Emergency Use Authorization by the FDA in late 2020, and more are likely to be authorized in the coming months. The resultant demand for vaccines and potential for manufacturing facilities and materials to be commandeered under the Defense Production Act of 1950, or equivalent foreign legislation, may make it more difficult to obtain materials or manufacturing slots for the products needed for our clinical trials or commercial products, which could lead to delays in these trials or issues with our commercial supply.

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 drug product 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. 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. Given our dependence on a limited number of CMOs to supply drug substance for our commercial products and clinical candidates, and our dependence on our own facility to produce patisiran formulated bulk drug product, any delay in supply caused by the COVID-19 pandemic, in particular at Agilent or at other facilities, could impact our ability to procure sufficient supplies for our approved products, and the development of our product candidates could also be delayed. Any delay or setback in the manufacture of our approved products could impede ongoing commercial supply, which could significantly impact our revenues and operating results. In addition, to the extent we or our partners rely on CMOs outside of the U.S. to supply drug substance for our product candidates, any delays or disruptions in supply caused by the COVID-19 pandemic could have a material adverse impact on the research and development activities and potential commercialization of our or our partners' product candidates.

The manufacturing process for our approved products 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, 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 any 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, 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 qualification 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 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 for any reason, including due to disruptions caused by the COVID-19 pandemic on their operations or at the sites they are overseeing, 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 additional revenues could be delayed.

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 additional employees as we focus on achieving our *Alnylam P^5x25* strategy. We face intense competition for qualified individuals from numerous pharmaceutical and biotechnology companies, universities, governmental entities and other research institutions, many of which have substantially greater resources with which to attract and reward qualified individuals than we do. In addition, due to the risks associated with developing a new class of medicine, we may face additional challenges in attracting and retaining employees. If we are not successful commercializing our approved products, we may be unable to attract and retain highly qualified sales and marketing professionals to support our approved products and our future products, if approved, including vutrisiran. 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 plans.

We may have difficulty expanding our operations successfully as we continue our evolution 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 our approved products, and increase the number of product candidates we are developing, we will need to continue to expand our operations in the U.S. and further develop 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 have global development and commercialization rights for ONPATTRO. In addition, we have received regulatory approval for our second RNAi therapeutic, GIVLAARI in the U.S., EU, Brazil, Canada and have also filed for marketing approval in Switzerland. In November 2020, we received regulatory approval for our third RNAi therapeutic, OXLUMO in the U.S. and EU. We plan to file for additional regulatory approvals for each of our commercially approved products in additional countries during 2021 and beyond.

From 2016 through 2020, we grew our workforce significantly and anticipate continuing to hire additional employees globally in the future as we focus on the commercialization of ONPATTRO, GIVLAARI and OXLUMO and achieving our *Alnylam P^5x25* strategy. 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 our approved products, 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 continue to expand, we will need to successfully manage additional relationships with various collaborators, suppliers, distributors 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 could give rise to liability.

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 our approved products, and we intend to do the same for our future products, if approved, including vutrisiran. 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 or interruption from computer viruses, unauthorized or inappropriate access or use, natural disasters, pandemics (including COVID-19), 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.

Following the results of a referendum in 2016, the United Kingdom, or UK, left the EU on January 31, 2020, commonly referred to as "Brexit." Pursuant to the formal withdrawal arrangements agreed between the UK and the EU, the UK was subject to a transition period until December 31, 2020, or the Transition Period, during which EU rules continued to apply, while the future relationship between the UK and EU was formally negotiated. The UK and the EU have signed a EU-UK Trade and Cooperation Agreement, which became provisionally applicable on January 1, 2021 and will become formally applicable once ratified by both the UK and the EU. This agreement provides details on how some aspects of the UK and EU's relationship will operate going forwards, however there are still many uncertainties. The long-term effects of Brexit will depend in part on how the EU-UK Trade and Cooperation Agreement, and any future agreements signed by the UK and the EU, take effect in practice. Such a withdrawal from the EU is unprecedented, and it is unclear how the restrictions on the UK's access to the European single market for goods, capital, services and labor within the EU and the wider commercial, legal and regulatory environment, could impact our current and future operations and clinical activities in the UK.

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. The uncertainty concerning the UK's legal, political and economic relationship with the EU following Brexit may also be a source of instability in the international markets, create significant currency fluctuations, and/or otherwise adversely affect trading agreements or similar cross-border co-operation arrangements (whether economic, tax, fiscal, legal, regulatory or otherwise). 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 and the Commercialization of Our Approved Products

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. We currently have multiple programs in clinical development, including internal and partnered programs in Phase 3 development, as well as several earlier-stage clinical programs. In January 2021, we announced positive topline results from the HELIOS-A Phase 3 study of vutrisiran, an investigational RNAi therapeutic in development for the treatment of ATTR amyloidosis. Based on these positive results, we expect to submit an NDA for vutrisiran with the FDA in early 2021. We also expect to submit an MAA in the EU

upon obtaining the topline results from the 18-month analysis, which are expected in late 2021. 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, such as our HELIOS-A study, 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, our approved products and our current product candidates, 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 to suspend dosing and the observation of an imbalance in mortality in revusiran-treated patients as compared to those on placebo.

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. 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, including the impact of public health emergencies such as the COVID-19 pandemic, 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, 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. More recently, in October 2020, Sanofi Genzyme announced that it voluntarily paused dosing in all ongoing fitusiran clinical studies to assess reports of non-fatal thrombotic events in patients participating in the ATLAS Phase 3 program. Following an assessment of available data and alignment with the FDA, in December 2020, Sanofi Genzyme has announced that it has resumed fitusiran dosing in ongoing adolescent and adult clinical studies.

As demonstrated by the discontinuation of our revusiran program in October 2016, the temporary suspension of dosing in September 2017 in our fitusiran studies, as well as Sanofi Genzyme's voluntary pause of fitusiran studies in October 2020, the occurrence of SAEs and/or AEs can result in the suspension or termination of clinical trials of a product candidate by us, our

partners, 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, including as a result of the COVID-19 pandemic;
- disruptions caused by man-made or natural disasters or public health pandemics or epidemics or other business interruptions, including the current COVID-19 pandemic;
- 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 or disruption or delays in the clinical supply due to the COVID-19 or a future pandemic;
- 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 or our partners may be unable to obtain U.S. or foreign regulatory approval for our or our partnered product candidates and, as a result, we or our partners may be unable to commercialize such product candidates.

Our and our partnered 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 and our partners 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 or our partners 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 or our partners 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 or our partners may submit. Moreover, the FDA may respond to these submissions by defining requirements we or our partners may not have anticipated. Such responses could lead to significant delays in the development of our or our partnered product candidates. In addition, because there may be approved treatments for some of the diseases for which we or our partners may seek approval, or treatments in development which are approved by the time we or they apply for approval, in order to receive regulatory approval, we or they 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. Interruption or delays in the operations of the FDA, EMA and comparable foreign regulatory agencies due to the COVID-19 pandemic, may impact the review, inspection and approval timelines for our or our partnered product candidates. For example, as of June 23, 2020, the FDA noted it is continuing to ensure timely reviews of applications for medical products during the COVID-19 pandemic in line with its user fee performance goals; however, the FDA may not be able to continue its current pace and approval timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the COVID-19 pandemic and travel restrictions the FDA is unable to complete such required inspections during the review period. In December 2020, the FDA issued a complete response letter regarding Novartis' NDA for inclisiran, stating that the agency could not approve the NDA by the PDUFA action date due to unresolved facility inspection-related conditions. Any such interruption or delay by the FDA, EMA or comparable foreign regulatory agency in light of COVID-19 pandemic could have a material adverse effect on our efforts to obtain regulatory approval for our product candidates, or our collaborator Novartis' efforts to obtain FDA approval for inclisiran, which could have a material adverse effect on our financial results.

Any delay or failure in obtaining required approvals for our product candidates or our partnered product candidates could have a material adverse effect on our ability to generate revenues from any product candidate for which we or our partners 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 or our partners 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 or our partners could be required to adopt a similar plan, known as a risk management plan, 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 our three approved drugs, 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 our approved drugs or other drug products required as a condition of approval or agreed to by us. The regulatory approvals that we receive for ONPATTRO, GIVLAARI and OXLUMO, as well as any regulatory approvals we receive for any other product candidates, including vutrisiran, 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 our approved products 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 our approved products may be more modest than originally anticipated;
- regulatory approvals for our approved products 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 our approved products, increase our expenses and impair our ability to successfully commercialize one or more of these products.

The CMO and manufacturing facilities we use to make our approved products and certain of our current product candidates, including our Cambridge facility, our 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 one or more of our products filed in other territories. The discovery of any new or previously unknown problems with our facilities or our CMOs, or our or their manufacturing processes or facilities, may result in restrictions on the drug or CMO or facility, including delay in approval or, in the future, withdrawal of the drug from the market. We have developed cGMP capabilities and processes for the manufacture of patisiran formulated bulk drug product for commercial use. In addition, in 2020, we completed 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 could 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 in several countries, which is administered subcutaneously, or tafamidis, marketed by Pfizer in several countries, 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.

We are an early-stage commercial company with recently 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 further establish our global commercial infrastructure. Even if we successfully scale our commercial capabilities, the market may not be receptive to our commercial products.

We are an early-stage commercial company, having received our first product approval only three years ago, and have established our capabilities for marketing, sales, market access and distribution over the last several years. We currently expect to rely on third parties to launch and market certain of our product candidates in certain geographies, if approved. However, we intend to commercialize ONPATTRO, GIVLAARI and OXLUMO, as well as several of our late-stage product candidates if approved, including 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, OXLUMO and, if approved, 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, OXLUMO and any future products, we will not be able to successfully commercialize our products without reliance on third parties.

The patient populations suffering from hATTR amyloidosis, AHP and PH1 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 these products may be adversely affected.

Our estimates regarding the potential market size for ONPATTRO, GIVLAARI, OXLUMO or any future products, including vutrisiran, 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, our efforts to raise disease awareness and improve diagnosis of hATTR

amyloidosis have been and may continue to be impacted by the COVID-19 pandemic. For example, Alnylam Act®, our third-party genetic screening initiative in the U.S., Canada and Brazil, experienced a decrease in submitted samples in the second quarter of 2020 as a result of the COVID-19 pandemic. 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, GIVLAARI and OXLUMO, 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 one or more of our approved products, 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 our approved products or any future products, including vutrisiran, 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. One or more of our approved products and other products for which we are able to obtain marketing approval, including vutrisiran, may not be considered cost-effective, and the amount reimbursed may be insufficient to allow us to sell such product(s) or any future products, including vutrisiran on a competitive basis. Increasingly, the third-party payors who reimburse patients or healthcare providers, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts reimbursed for drug products. In the U.S., we have entered into at least 30 VBAs and are negotiating additional VBAs with commercial health insurers. 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, and the agreements are structured to link our approved products' performance in real-world use to financial terms. Partnering with payers on these agreements is intended to provide more certainty to them for their investment and help accelerate coverage decisions for patients. If the prices we are able to charge for our products, 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, GIVLAARI and OXLUMO. 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. On July 24, 2020, President Trump signed four Executive Orders aimed at lowering drug prices. The Executive Orders direct the Secretary of Health and Human Services to: eliminate protection under an Anti-Kickback Statute safe harbor for certain retrospective price reductions provided by drug manufacturers to sponsors of Medicare Part D plans or pharmacy benefit managers that are not applied at the point-of-sale; allow the importation of certain drugs from other countries through individual waivers, permitting the re-importation of insulin products, and prioritizing finalization of the proposed rule to permit the importation of drugs from Canada; depending on whether pharmaceutical manufacturers agree to other measures, ensure that payment by the Medicare program for certain Medicare Part B drugs is not higher than the payment by other designated countries; and allow certain low-income individuals receiving insulin and epinephrine purchased by a Federally Qualified Health Center, or FQHC, as part of the 340B drug program to purchase those drugs at the discounted price paid by the FQHC. On September 13, 2020, President Trump signed an Executive Order that directs the Secretary of Health and Human Services to immediately "take appropriate steps to implement rulemaking" to test a demonstration project through the CMS Innovation Center whereby Medicare Part B reimbursement for "certain high-cost prescriptions drugs" would be no more than most-favored-nation price (i.e., the lowest price) after adjustments, for a pharmaceutical product that the drug manufacturer sells in a member country of the Organization for Economic Cooperation and Development that has a comparable per-capita gross domestic product. On November 20, 2020, CMS issued an interim final rule implementing President Trump's most favored nation executive order, effective January 1, 2021. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the Medicare Modernization Act, or MMA, contains provisions that call for the promulgation of regulations that expand pharmacists' and wholesalers' ability to import cheaper versions of an approved drug and competing products from Canada, where there are government price controls. Further, the MMA provides that these provisions, as codified under section 804 of the FDCA, will not take effect, unless and until the Secretary of the HHS certifies that the implementation of the provisions will pose no additional risk to the public's health and safety and will result in a significant reduction in the cost of products to American consumers. On September 23, 2020, the Secretary of the HHS made such certification to Congress, and on October 1, 2020, the FDA published a final rule that allows for the importation of certain prescription drugs from Canada. However, certain categories of drug products are excluded from the definition of "prescription drug" that can potentially be imported from Canada, including intravenously injected drugs, such as ONPATTRO. Under the final rule, States and Indian tribes, and in certain future circumstances pharmacists and wholesalers, may submit importation program proposals to the FDA for review and authorization. Several States, such as Florida, have taken steps to draft and submit importation program proposals to FDA for review and approval. On September 25, 2020, CMS stated drugs imported by States under this rule will not be eligible for federal rebates under Section 1927 of the Social Security Act and manufacturers would not report these drugs for "best price" or Average Manufacturer Price purposes. Since these drugs are not considered covered outpatient drugs, CMS further stated it will not publish a National Average Drug Acquisition Cost for these drugs. Separately, the FDA

also issued a final guidance document outlining a 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 market implications of the notice of Executive Orders and the final rule and guidance are unknown at this time, and a lawsuit has been filed in a federal court to challenge the final rule, but legislation, regulations or policies allowing the importation or 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 our approved products, 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 could, directly or indirectly, affect our ability to sell ONPATTRO, GIVLAARI, OXLUMO or future products, if approved, including vutrisiran, 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 the Centers for Medicare and Medicaid Services, or 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 2030; however, pursuant to the CARES Act, and subsequent legislation, these Medicare sequester reductions have been suspended from May 1, 2020 through March 31, 2021 due to the COVID-19 pandemic. Proposed legislation, if passed, would extend this suspension until the end of the COVID-19 pandemic. 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 our approved products or any of our product candidates for which we may obtain regulatory approval, including vutrisiran, or the frequency with which our products or any future product, including vutrisiran, 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. Although some 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, at the federal level, the U.S. government's budget proposal for fiscal year 2021 includes a $135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the U.S. government sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Likewise, the Biden administration has indicated that lowering prescription drug prices is a priority, but we do not yet know what steps the administration will take or whether such steps will be successful.

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 one or more of our approved products 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. Failure to comply 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 to conduct clinical trials outside of the U.S., 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.

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 our approved products or any future products, including vutrisiran, 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 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 providers 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.

In addition to the above, on November 20, 2020, the Office of Inspector General, or OIG finalized further modifications to the federal Anti-Kickback Statute. Under the final rules, OIG added safe harbor protections under the Anti-Kickback Statute for certain coordinated care and value-based arrangements among clinicians, providers, and others. The final rule (with some exceptions) became effective January 19, 2021. We continue to evaluate what effect, if any, these rules will have on our business.

Some state laws also require pharmaceutical manufacturers to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, in addition to requiring manufacturers to report information related to payments to physicians and other healthcare 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 (including individual imprisonment), 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 OIG, any of which could adversely affect our financial results. We are continuing to establish our global compliance infrastructure following the commercial launch of our three products over the last three years in the U.S., EU and multiple other geographies, and as we prepare for the launch of our products 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 our approved products, 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.

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 (however, these Medicare sequester reductions have been suspended from May 1, 2020 through December 31, 2020 due to the COVID-19 pandemic). 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 Bipartisan Budget Act of 2018,

these reductions will stay in effect through 2030 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 our approved products and any other products we may develop, including vutrisiran.

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. In addition, product liability claims could result in an FDA investigation of the safety and effectiveness of our approved 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 our approved products. 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 one or more of our or our partner's approved products, or further develop and commercialize future products, or continue 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, Stanford University, 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, Arbutus and Dicerna. 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, our late-stage therapeutic candidates being developed by us or our licensees, including vutrisiran, 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, or further develop and commercialize future products such as 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, GIVLAARI or OXLUMO, 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.

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 or legal proceeding 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 our approved products 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 was 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 claimed it was owed technology access fees, or TAF's, 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. The hearing portion of the arbitration process was completed in June 2020, and post-hearing briefing was completed in the third quarter of 2020. On October 23, 2020, a partial award was issued by the arbitration panel seeking additional information from us. The arbitration panel issued its final award in December 2020, which ruled in favor of Ionis's request for a TAF on certain rights the panel determined we received in the Sanofi restructuring (but rejecting the TAF amount sought by Ionis), and in favor of us in denying Ionis's request for a TAF on a milestone payment received by us in the same restructuring. The panel's final award also denied Ionis's request for pre-judgement interest and attorney's fees. Pursuant to the panel's final award, we paid $41.2 million to Ionis in January 2021. Please read Note 12 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 additional information regarding this matter.

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 each of our approved products 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 such products. 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 and commercialize. 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 authorization 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 approved in a number of jurisdictions, and inotersen, developed and marketed by Ionis, as well as product candidates in various stages of clinical development, including an additional investigational drug. Finally, we are aware that Eidos Therapeutics, Inc., or Eidos, initiated a Phase 3 clinical trial of acoramidis, a TTR stabilizer, in ATTR-CM in February 2019, and completed enrollment of the Phase 3 clinical trial in ATTR-CM in late 2020. Eidos anticipates topline results from the ATTR-CM trial in late 2021 or early 2022. Eidos also initiated enrollment in a Phase 3 clinical trial of acoramidis in ATTR-PN patients in the fourth quarter of 2020. While we believe that ONPATTRO has and will continue to have a competitive product profile, and if approved, that vutrisiran will have a competitive product profile, it is possible that ONPATTRO and/or vutrisiran may 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 OXLUMO, our RNAi therapeutic approved in the U.S. and EU 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 3 development for primary or severe secondary hyperoxaluria by Allena Pharmaceuticals, Inc., and nedosiran, an investigational RNAi therapeutic in development by Dicerna for the treatment of PH. In July 2019, the FDA granted a Breakthrough Therapy Designation to nedosiran for the treatment of patients with PH, and in January 2021, Dicerna announced that it completed enrollment in its PHYOX2 pivotal clinical trial of nedosiran with topline results expected in mid-2021. In April 2020, we and Dicerna granted each other a non-exclusive cross-license to our respective intellectual property related to lumasiran, and Dicerna's nedosiran product candidate. 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, 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 (acquired by Ionis in October 2020) has received marketing approval for an antisense drug, inotersen that was developed by Ionis, for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with 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. For example, the trading price for our common stock and the common stock of other biopharmaceutical companies was highly volatile during the initial stages of the COVID-19 pandemic. The COVID-19 pandemic has continued to evolve, and the extent to which the pandemic may impact our business will depend on future developments, which are highly uncertain and cannot be predicted with confidence. 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. 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 amended, or the Complaint, 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. On March 23, 2020, the Court granted our motion and dismissed the Complaint without prejudice. Pursuant to a prior Order of the Court, on June 1, 2020, plaintiff filed a motion seeking leave to file a further amended complaint. That motion was fully briefed on June 22, 2020, and remains pending with the Court. We believe that the allegations contained in the now dismissed Complaint are without merit. 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, in excess of our insurance coverage, 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 alleging 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, or the New York State Securities Litigation. We believe the allegations in the New York State Securities Litigation, like those in the Complaint described above, are without merit and we intend to defend the case vigorously. This litigation and 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, 2020, our seven 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; Maidenhead, United Kingdom; and Tokyo, Japan. A description of certain of the facilities we lease or own as of January 31, 2021 is included in the table below.

Location	Primary Use	Approximate Square Footage	Lease Expiration Date	Renewal Option
675 West Kendall Street Henri A. Termeer Square 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	March 2024 and June 2026	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, Switzerland	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
Pacific Century Place 1-Chome-11-1 Marunouchi Chiyoda-ku Tokyo, Japan	Office space	16,900	May 2025	None

* We lease office space located on the 12th, 13th and 16th floors at 101 Main Street, Cambridge, Massachusetts under a non-cancelable real property lease agreement by and between the Company and RREEF America REIT II CORP. PPP, dated as of April 15, 2015, or Lease. On September 30, 2020, we entered into a First Amendment to Lease, pursuant to which the term of the Lease with respect to the 12th and 13th floors was extended for an additional five years, through June 30, 2026. The term of the Lease, as amended, shall expire and be terminated solely as to the 16th floor on June 30, 2021. In addition, we have a separate lease agreement for the 10th floor at 101 Main Street, which expires in March 2024.

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

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 12, 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 29, 2021, there were 27 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

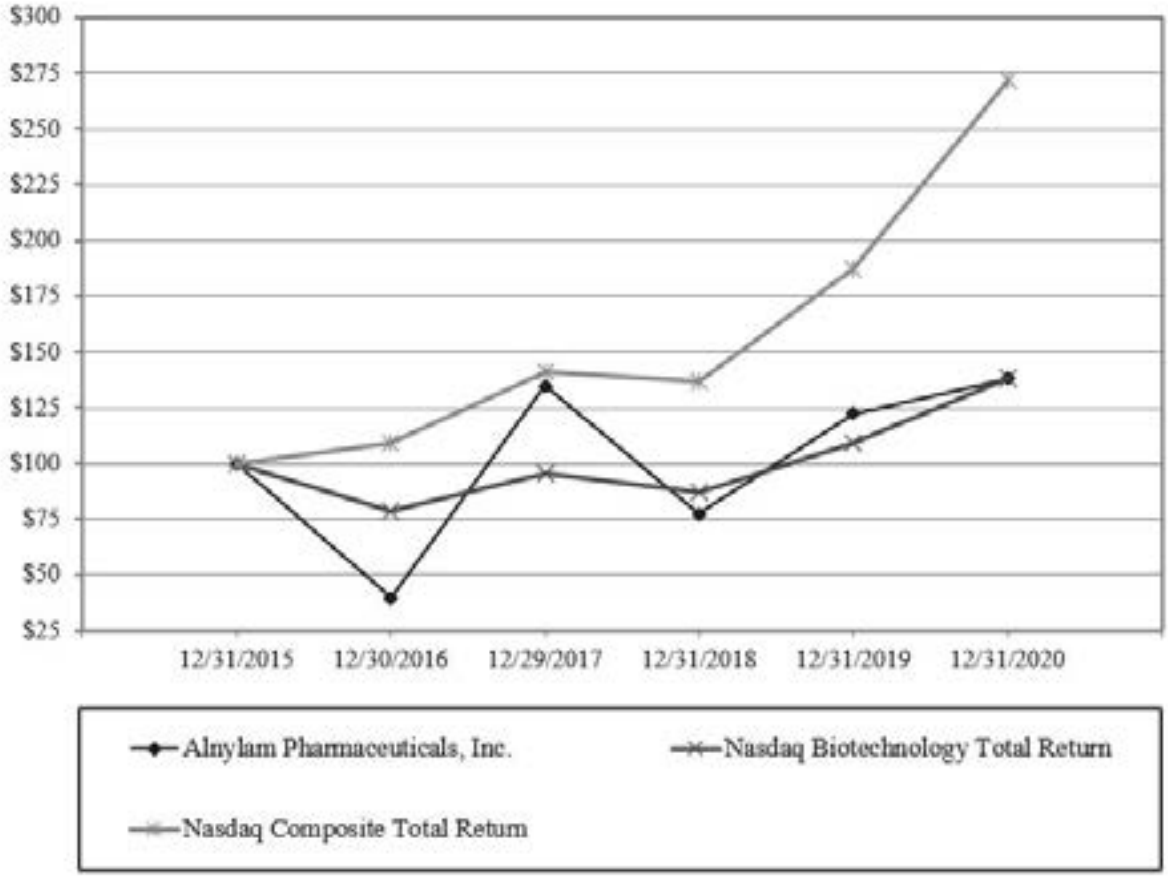
We intend to file with the SEC a definitive Proxy Statement, which we refer to herein as the Proxy Statement, not later than 120 days after the close of the fiscal year ended December 31, 2020. The information required by this item relating to our equity compensation plans is incorporated herein by reference 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 the last trading day of 2015, to the close of the last trading day of 2020, 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



	12/31/2015	12/30/2016	12/29/2017	12/31/2018	12/31/2019	12/31/2020
Alnylam Pharmaceuticals, Inc.	$ 100.00	$ 39.77	$ 134.96	$ 77.45	$ 122.34	$ 138.06
Nasdaq Composite Total Return	$ 100.00	$ 108.87	$ 141.13	$ 137.12	$ 187.44	$ 271.64
Nasdaq Biotechnology Total Return	$ 100.00	$ 78.65	$ 95.67	$ 87.19	$ 109.08	$ 137.90

ITEM 6. SELECTED CONSOLIDATED FINANCIAL DATA

The following selected consolidated financial data for each of the five years in the period ended December 31, 2020 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,				
	2020	2019	2018 (2)	2017	2016
Statements of Operations Data:					
Revenues	$ 492,853	$ 219,750	$ 74,908	$ 89,912	$ 47,159
Operating costs and expenses (1)	1,321,291	1,159,181	889,581	590,000	471,746
Loss from operations	(828,438)	(939,431)	(814,673)	(500,088)	(424,587)
Net loss	$ (858,281)	$ (886,116)	$ (761,497)	$ (490,874)	$ (410,108)
Net loss per common share — basic and diluted	$ (7.46)	$ (8.11)	$ (7.57)	$ (5.42)	$ (4.79)
Weighted-average common shares outstanding — basic and diluted	114,986	109,264	100,590	90,554	85,596
(1) Stock-based compensation expenses included in operating costs and expenses	$ 139,873	$ 174,841	$ 157,752	$ 92,819	$ 75,528

(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,” in our annual report on Form 10-K for the fiscal year ended December 31, 2019 that was filed with the SEC on February 13, 2020 for further discussion of our adoption of the revenue standard.

	December 31,				
	2020	2019	2018	2017	2016 (1)
Balance Sheet Data:					
Cash, cash equivalents and marketable securities	$1,874,395	$1,536,162	$1,084,155	$1,704,537	$ 942,601
Restricted investments	40,725	14,825	44,825	30,000	150,000
Working capital	2,029,507	1,363,270	1,021,202	1,620,489	540,178
Total assets	3,407,061	2,395,134	1,574,802	1,994,730	1,262,810
Liability related to the sale of future royalties, net of current portion (Note 5)	1,058,225	—	—	—	—
Long-term debt	191,278	—	30,000	30,000	150,000
Total stockholders’ equity	1,016,247	1,438,692	1,301,965	1,766,431	920,221

(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 commercial 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 four products that have received marketing approval, including one partnered product, and six late-stage investigational programs advancing towards potential commercialization. In Part I, Item 1. "Business" you can also find a summary of key events in 2020 and 2021 to-date related to our marketed products and our clinical development programs.

We have incurred significant losses since we commenced operations in 2002 and as of December 31, 2020, we had an accumulated deficit of $4.59 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, however we expect 2019 represents our peak

non-GAAP operating loss year as we transition towards a self-sustainable financial profile. We anticipate that our operating results will continue to 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. In November 2020, we received FDA and EC approval for our third product, OXLUMO and began to generate net revenues from product sales during the fourth quarter of 2020. 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, OXLUMO 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, Vir, Sanofi Genzyme and Novartis. In addition to revenues from the commercial sales of ONPATTRO, GIVLAARI, OXLUMO 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, including our strategic financing collaboration with Blackstone. Such alliances may include license and other fees, funded research and development, milestone payments and royalties on product sales by our licensors, including royalties on sales of Leqvio made by our partner Novartis, as well as proceeds from our term loan facility or 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 revenues 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.

We record reserves, based on contractual terms, for 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. The following are the components of variable consideration related to product revenues:

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 within each customer agreement. 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.

Net Revenues from Collaborations

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, Net Revenues from Collaborations, 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 (less than 12 months) or long-term (more than 12 months) deferred revenue based on our best estimate of when such revenue will be recognized.

Liability Related to the Sale of Future Royalties

We account for the liability related to the sale of future royalties as a debt financing, as we have significant continuing involvement in the generation of the cash flows. Interest on the liability related to the sale of future royalties will be recognized using the effective interest rate method over the life of the related royalty stream.

The liability related to the sale of future royalties and the related interest expense are based on our current estimates of future royalties and commercial milestones expected to be paid over the life of the arrangement, which we determine by using third-party forecasts of inclisiran's global net revenue. We will periodically assess the expected payments and to the extent the amount or timing of our future estimated payments is materially different than our previous estimates, we will account for any such change by adjusting the liability related to the sale of future royalties and prospectively recognizing the related non-cash interest expense.

Results of Operations

The following data summarizes the results of our operations:

(In thousands)	Year Ended December 31, 2020	2019	2018
Revenues	$ 492,853	$ 219,750	$ 74,908
Operating costs and expenses	$ 1,321,291	$ 1,159,181	$ 889,581
Loss from operations	$ (828,438)	$ (939,431)	$ (814,673)
Net loss	$ (858,281)	$ (886,116)	$ (761,497)

For discussion of our 2019 results and a comparison with 2018 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, 2019 that was filed with the SEC on February 13, 2020.

Revenues

The following table summarizes our total consolidated revenues:

(In thousands, except percentages)	Years Ended December 31, 2020	2019	2018	2020 vs 2019 Dollar Change	Percent Change	2019 vs 2018 Dollar Change	Percent Change
Net product revenues	$ 361,520	$ 166,537	$ 12,535	$ 194,983	117 %	$ 154,002	1,229 %
Net revenues from collaborations	131,333	53,213	62,373	78,120	147 %	(9,160)	(15)%
Total	$ 492,853	$ 219,750	$ 74,908	$ 273,103	124 %	$ 144,842	193 %

Net Product Revenues

Net product revenues consist of the following:

(In thousands, except percentages)	Year Ended December 31, 2020	2019	2018	2020 vs 2019 Dollar Change	Percent Change	2019 vs 2018 Dollar Change	Percent Change
ONPATTRO							
United States	$ 151,574	$ 116,302	$ 8,589	$ 35,272	30 %	$ 107,713	1,254 %
Europe	107,755	43,980	3,946	63,775	145 %	40,034	1,015 %
Rest of World (primarily Japan)	46,752	6,105	—	40,647	666 %	6,105	N/A
Total	$ 306,081	$ 166,387	$ 12,535	$ 139,694	84 %	$ 153,852	1,227 %
GIVLAARI							
United States	$ 42,797	$ 150	$ —	$ 42,647	28,431 %	$ 150	N/A
Europe	12,000	—	—	12,000	N/A	—	N/A
Rest of World	309	—	—	309	N/A	—	N/A
Total	$ 55,106	$ 150	$ —	$ 54,956	36,637 %	$ 150	N/A
OXLUMO							
Europe	$ 333	$ —	$ —	$ 333	N/A	$ —	N/A
Total net product revenues	$ 361,520	$ 166,537	$ 12,535	$ 194,983	117 %	$ 154,002	1,229 %

Net product revenues increased during the year ended December 31, 2020, compared to the year ended December 31, 2019, as a result of the continued, global expansion of ONPATTRO and GIVLAARI into additional major markets, an entire year of GIVLAARI revenues following commercial launch in the U.S. in the fourth quarter of 2019, and net product revenues from OXLUMO sales following regulatory approval in the fourth quarter of 2020.

We expect net product revenues to increase during 2021 as compared to 2020 as we continue to add new patients onto our commercial products, 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, 2020 and 2019.

Net Revenues from Collaborations

The following table summarizes our total consolidated net revenues from collaborations under our research and development collaboration agreements:

	Years Ended December 31,			2020 vs 2019		2019 vs 2018	
(In thousands, except percentages)	2020	2019	2018	Dollar Change	Percent Change	Dollar Change	Percent Change
Regeneron Pharmaceuticals	$ 74,072	$ 26,075	$ —	$ 47,997	184 %	$ 26,075	N/A
Vir Biotechnology	31,396	12,809	12,778	18,587	145 %	31	— %
The Medicines Company (acquired by Novartis AG)	22,208	2,315	2,789	19,893	859 %	(474)	(17)%
Sanofi Genzyme	995	10,976	46,000	(9,981)	(91)%	(35,024)	(76)%
Other	2,662	1,038	806	1,624	156 %	232	29 %
Total	$ 131,333	$ 53,213	$ 62,373	$ 78,120	147 %	$ (9,160)	(15)%

Net revenues from collaborations increased during the year ended December 31, 2020, as compared to the year ended December 31, 2019, primarily due to an increase in revenue recognized in connection with our collaboration agreements with Regeneron and Vir as a result of increased activities and with Novartis, as well as of the achievement of certain milestones, partially offset by a decrease in activities in connection with our collaboration agreements with Sanofi.

We expect net revenues from collaborations to increase during 2021, as compared to 2020, primarily due to increased reimbursable activities, the anticipated achievement of milestones under our collaboration agreements with Regeneron, Vir and Novartis in addition to royalty revenues recognized under our Novartis agreement associated with the commercialization of Leqvio® (inclisiran) in the EU and potentially other geographies assuming regulatory approval.

Operating Costs and Expenses

The following table summarizes our operating costs and expenses:

	Year Ended December 31,			2020 vs 2019		2019 vs 2018	
(In thousands, except percentages)	2020	2019	2018	Dollar Change	Percent Change	Dollar Change	Percent Change
Cost of goods sold	$ 78,052	$ 25,062	$ 1,802	$ 52,990	211 %	$ 23,260	1,291 %
Research and development	654,819	655,114	505,420	(295)	— %	149,694	30 %
Selling, general and administrative	588,420	479,005	382,359	109,415	23 %	96,646	25 %
Total	$1,321,291	$1,159,181	$ 889,581	$ 162,110	14 %	$ 269,600	30 %

Cost of Goods Sold

Cost of goods sold increased during the year ended December 31, 2020, as compared to the year ended December 31, 2019, primarily due to increased third-party royalties and increased sales of capitalized inventory associated with both our net product revenues and product supply under our collaboration agreements. During the year ended December 31, 2020, product sold and recognized as revenue was substantially from capitalized inventory, whereas during 2019, the majority of the units of product sold and recognized as revenue were zero-cost inventory. We will continue to sell our zero-cost inventory of GIVLAARI in 2021.

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 2021, as compared to 2020, primarily as a result of an increase in net product revenues and net revenues from collaborations, as well as an increase in sales of capitalized inventory.

Research and Development

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

(In thousands, except percentages)	Year Ended December 31, 2020	2019	2018	2020 vs 2019 Dollar Change	Percent Change	2019 vs 2018 Dollar Change	Percent Change
Clinical trial and manufacturing	$ 218,752	$ 203,897	$ 173,271	$ 14,855	7 %	$ 30,626	18 %
Compensation and related	190,705	157,001	116,350	33,704	21 %	40,651	35 %
External services	70,120	75,448	55,165	(5,328)	(7)%	20,283	37 %
Facilities-related	69,769	54,650	42,159	15,119	28 %	12,491	30 %
Stock-based compensation	60,464	88,930	80,509	(28,466)	(32)%	8,421	10 %
Lab supplies, materials and other	42,229	38,158	30,007	4,071	11 %	8,151	27 %
License fees	2,780	37,030	7,959	(34,250)	(92)%	29,071	365 %
Total	$ 654,819	$ 655,114	$ 505,420	$ (295)	— %	$ 149,694	30 %

Research and development expenses were relatively consistent during the year ended December 31, 2020, as compared to the year ended December 31, 2019, primarily due to offsetting increases and decreases of expenses, as follows:

- Increased compensation and related expenses and facilities-related expenses, as a result of increased headcount to support long-term strategic growth; and
- Increased clinical trial and manufacturing expenses as a result of increased services related to the advancement of our early and late-stage programs to support long-term strategic growth.

Offset by:

- Decreased stock-based compensation primarily due to the achievement of certain performance-based milestones in 2019; and
- Decreased license fees relative to license fees associated with the execution of our collaboration agreement with Regeneron in 2019 and certain regulatory milestones achieved in 2019.

During the years ended December 31, 2020 and 2019, 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, 2020	2019	2018
Regeneron Pharmaceuticals	$ 57,833	$ 24,916	$ —
Vir Biotechnology	30,644	15,479	16,071
Sanofi Genzyme	2,957	13,856	43,219
The Medicines Company (acquired by Novartis AG)	1,699	2,721	1,869
Other	—	—	3,247
Total	$ 93,133	$ 56,972	$ 64,406

Selling, General and Administrative

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

	Year Ended December 31,			2020 vs 2019		2019 vs 2018	
(In thousands, except percentages)	**2020**	**2019**	**2018**	**Dollar Change**	**Percent Change**	**Dollar Change**	**Percent Change**
Compensation and related	$ 200,071	$ 148,271	$ 107,376	$ 51,800	35 %	$ 40,895	38 %
Consulting and professional services	176,097	155,843	137,201	20,254	13 %	18,642	14 %
Stock-based compensation	79,409	85,911	77,243	(6,502)	(8)%	8,668	11 %
Facilities-related	45,387	35,779	25,658	9,608	27 %	10,121	39 %
Other	87,456	53,201	34,881	34,255	64 %	18,320	53 %
Total	$ 588,420	$ 479,005	$ 382,359	$ 109,415	23 %	$ 96,646	25 %

Selling, general and administrative expenses increased during the year ended December 31, 2020, as compared to the year ended December 31, 2019, 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 growth, as well as the continued expansion of our commercial products into additional major markets; and
- Increased other expenses primarily due to a change in an estimated accrual for a contingent liability related to our arbitration with Ionis.

We expect that research and development expenses combined with selling, general and administrative expenses will increase during 2021, as compared to 2020, as we continue to develop our pipeline, advance our product candidates, including partnered programs, into later-stage development, prepare regulatory submissions and continue to build-out our global commercial infrastructure and field team to support ONPATTRO, GIVLAARI, OXLUMO and potentially additional product launches. 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.

Total Other (Expense) Income

Total other (expense) income consists of the following:

(In thousands, except percentages)	Year Ended December 31, 2020	2019	2018	2020 vs 2019 Dollar Change	Percent Change	2019 vs 2018 Dollar Change	Percent Change
Interest expense	$(84,496)	$ —	$ —	$(84,496)	N/A	$ —	N/A
Interest income	11,809	33,448	29,262	(21,639)	(65)%	4,186	14 %
Other income:							
Realized and unrealized gains on marketable equity securities	54,042	11,288	3,564	42,754	379 %	7,724	N/A
Change in fair value of development derivative liability	(17,185)	—	—	(17,185)	N/A	—	N/A
Change in fair value of liability obligation	—	9,422	—	(9,422)	(100)%	9,422	N/A
Gain on litigation settlement	—	—	20,564	—	N/A	(20,564)	(100)%
Other income	8,668	20	609	8,648	43,240 %	(589)	(97)%
Total	$(27,162)	$ 54,178	$ 53,999	$(81,340)	(150)%	$ 179	— %

Total other expense increased during the year ended December 31, 2020, as compared to the year ended December 31, 2019, primarily due to the following:

- $84.5 million of interest expense associated with the sale of future royalties;
- Decreased interest income of $21.6 million as a result of lower interest rates;
- Loss of $17.2 million as a result of a mark-to-market adjustment related to the development derivative liability; and

Offset by:

- Increased other income due to realized and unrealized gains in marketable equity securities.

Liquidity and Capital Resources

The following table summarizes our cash flow activities:

(In thousands)	Year Ended December 31, 2020	2019	2018
Net loss	$ (858,281)	$ (886,116)	$ (761,497)
Non-cash adjustments to reconcile net loss to net cash used in operating activities:	256,021	205,308	153,782
Changes in operating assets and liabilities:	(12,701)	402,381	45,099
Net cash used in operating activities	(614,961)	(278,427)	(562,616)
Net cash (used in) provided by investing activities	(435,518)	(417,677)	272,945
Net cash provided by financing activities	994,979	823,184	65,470
Effect of exchange rate changes on cash, cash equivalents and restricted cash	4,918	(83)	—
Net (decrease) increase in cash, cash equivalents and restricted cash	(50,582)	126,997	(224,201)
Cash, cash equivalents and restricted cash, beginning of period	549,628	422,631	646,832
Cash, cash equivalents and restricted cash, end of period	$ 499,046	$ 549,628	$ 422,631

Since we commenced operations in 2002, we have generated significant losses and as of December 31, 2020, we had an accumulated deficit of $4.59 billion. As of December 31, 2020, we had cash, cash equivalents and marketable securities of $1.87 billion, compared to $1.54 billion as of December 31, 2019.

Operating Activities

Net cash used in operating activities increased during the year ended December 31, 2020, compared to the year ended December 31, 2019, primarily due to the receipt of $400.0 million in May 2019 for the upfront payment associated with our strategic collaboration with Regeneron resulting in an increase to deferred revenue.

Investing Activities

Net cash used in investing activities increased during the year ended December 31, 2020, compared to the year ended December 31, 2019, primarily due to a net increase in our marketable debt securities and restricted investment activities offset by a decrease in capital expenditures primarily related to our Norton manufacturing facility.

Financing Activities

Net cash provided by financing activities increased during the year ended December 31, 2020, compared to the year ended December 31, 2019, primarily due to $500.0 million received from our sale to Blackstone of one-half of our royalty interest under the MDCO agreement in April 2020, increased net proceeds of $129.2 million from the issuance of common stock in connection with stock option exercises and other types of equity and proceeds of $200.0 million in connection with the first draw down on our credit agreement, compared to the prior year proceeds of $400.0 million from our issuance of common stock to Regeneron in April 2019 and $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, as of December 31, 2020, have received regulatory approval and commercially launched three products: ONPATTRO, GIVLAARI and OXLUMO. In early 2021, we announced *Alnylam P^5x25,* which is aimed at our planned transition to a top 5 biotech in market capitalization. As part of this strategy, our goal is to achieve sustainable non-GAAP profitability by the end of 2025. 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 losses 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, manufacturing and commercial capabilities, including global operations, continued management and growth of our intellectual property including our patent portfolio, collaborations and general corporate activities.

Based on our current operating plan, we believe that our cash, cash equivalents and marketable securities as of December 31, 2020, together with the cash we expect to generate from product sales and under our current alliances, in addition to our strategic financing collaboration with The Blackstone Group Inc. and certain of its affiliates, 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. However, due to numerous factors described in more detail under the caption Part I, Item 1A, "Risk Factors" of this annual report on Form 10-K, we may require significant additional funds earlier than we currently expect in order to continue to commercialize ONPATTRO, GIVLAARI and OXLUMO, and to develop, conduct clinical trials for, manufacture and, if approved, commercialize additional product candidates.

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, 2020. 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				
(In thousands)	2021	2022 and 2023	2024 and 2025	After 2025	Total
Facility lease obligations (1)	$ 38,593	$ 90,156	$ 84,108	$ 323,473	$ 536,330
Long-term debt	—	—	—	200,000	200,000
Total contractual cash obligations	$ 38,593	$ 90,156	$ 84,108	$ 523,473	$ 736,330

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

The table above excludes approximately $441.4 million of commitments related to clinical and manufacturing-related agreements, as they are cancellable. The table above also excludes payments under our purchase and sale and funding agreements with Blackstone, as such payments are contingent on either future sales or the successful achievement of certain development and regulatory events. 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 are immaterial in connection with our various collaboration 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, 2020, 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, 2020 and 2019, 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

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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, 2020 and 2019, 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, 2020, 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, 2020, 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, 2020 and 2019, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2020 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, 2020, 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.

Liability Related to Sale of Future Royalties and Commercial Milestones

As described in Notes 2 and 5 to the consolidated financial statements, the liability related to the sale of future royalties and the related interest expense are based on management's current estimates of future royalties and commercial milestones expected to be paid over the life of the arrangement. Interest on the liability related to the sale of future royalties will be recognized using the effective interest rate method, resulting in the recognition of interest expense. Management periodically assesses the expected payments and to the extent the amount or timing of the future estimated payments is materially different than the previous estimates, management accounts for any such change by adjusting the liability related to the sale of future royalties and prospectively recognizing the related non-cash interest expense. Management's estimate of the amount of expected future payments to Blackstone over the life of the arrangement is based on the estimated global net sales of inclisiran. The Company recorded a liability related to the sale of future royalties of $1.07 billion as of December 31, 2020 and recognized interest expense on the liability related to the sale of future royalties of $84.5 million for the year ended December 31, 2020.

The principal considerations for our determination that performing procedures relating to the liability related to the sale of future royalties and commercial milestones is a critical audit matter are the significant judgment by management when developing the estimate of the timing and amount of future royalties and commercial milestones to be paid. This in turn led to a high degree of auditor judgment and effort in performing procedures and in evaluating audit evidence relating to management's estimate of the expected future royalties and commercial milestones to be paid and the selection of third party data used to estimate global net sales of inclisiran.

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 liability for future royalties and commercial milestones, including controls over management's process for developing the estimate of timing and amount of future royalties and commercial milestones to be paid. These procedures also included, among others (i) testing management's process for developing the estimate of timing and amount of future royalties and commercial milestones to be paid and (ii) evaluating the reasonableness of significant assumptions used by management when developing the estimate of expected future royalties and commercial milestones to be paid related to the selection of third party data used to estimate global net sales of inclisiran. Evaluating management's assumption related to the selection of third-party data used to estimate global net sales of inclisiran involved evaluating whether the assumptions used by management were reasonable considering consistency with industry data.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
February 11, 2021

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

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

	December 31,	
	2020	2019
ASSETS		
Current assets:		
Cash and cash equivalents	$ 496,580	$ 547,178
Marketable debt securities	1,333,182	975,017
Marketable equity securities	44,633	13,967
Accounts receivable, net	102,413	43,011
Inventory	75,202	56,348
Prepaid expenses and other current assets	62,767	80,343
Receivable related to the sale of future royalties	500,000	—
Total current assets	2,614,777	1,715,864
Property, plant and equipment, net	465,029	425,179
Operating lease right-of-use assets	241,485	221,197
Restricted investments	40,725	14,825
Other assets	45,045	18,069
Total assets	$ 3,407,061	$ 2,395,134
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 51,966	$ 49,884
Accrued expenses	355,909	197,201
Operating lease liability	36,872	27,688
Deferred revenue	127,207	77,821
Liability related to the sale of future royalties	13,316	—
Total current liabilities	585,270	352,594
Operating lease liability, net of current portion	293,039	276,135
Deferred revenue, net of current portion	225,094	318,383
Long-term debt	191,278	—
Liability related to the sale of future royalties, net of current portion	1,058,225	—
Other liabilities	37,908	9,330
Total liabilities	2,390,814	956,442
Commitments and contingencies (Note 12)		
Stockholders' equity:		
Preferred stock, $0.01 par value per share, 5,000 shares authorized and no shares issued and outstanding as of December 31, 2020 and December 31, 2019	—	—
Common stock, $0.01 par value per share, 250,000 and 250,000 shares authorized as of December 31, 2020 and December 31, 2019, respectively; 116,427 shares issued and outstanding as of December 31, 2020; 112,188 shares issued and outstanding as of December 31, 2019	1,164	1,122
Additional paid-in capital	5,644,074	5,201,176
Accumulated other comprehensive loss	(43,622)	(36,518)
Accumulated deficit	(4,585,369)	(3,727,088)
Total stockholders' equity	1,016,247	1,438,692
Total liabilities and stockholders' equity	$ 3,407,061	$ 2,395,134

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,		
	2020	2019	2018
Statements of Operations			
Revenues:			
Net product revenues	$ 361,520	$ 166,537	$ 12,535
Net revenues from collaborations	131,333	53,213	62,373
Total revenues	492,853	219,750	74,908
Operating costs and expenses:			
Cost of goods sold	78,052	25,062	1,802
Research and development	654,819	655,114	505,420
Selling, general and administrative	588,420	479,005	382,359
Total operating costs and expenses	1,321,291	1,159,181	889,581
Loss from operations	(828,438)	(939,431)	(814,673)
Other (expense) income:			
Interest expense	(84,496)	—	—
Interest income	11,809	33,448	29,262
Other income, net	45,525	20,730	24,737
Total other (expense) income	(27,162)	54,178	53,999
Loss before income taxes	(855,600)	(885,253)	(760,674)
Provision for income taxes	(2,681)	(863)	(823)
Net loss	$ (858,281)	$ (886,116)	$ (761,497)
Net loss per common share — basic and diluted	$ (7.46)	$ (8.11)	$ (7.57)
Weighted-average common shares used to compute basic and diluted net loss per common share	114,986	109,264	100,590
Statements of Comprehensive Loss			
Net loss	$ (858,281)	$ (886,116)	$ (761,497)
Other comprehensive (loss) income:			
Unrealized gain on marketable securities	211	558	1,220
Foreign currency translation loss	(7,081)	(343)	—
Defined benefit pension plans, net of tax	(234)	(3,520)	—
Comprehensive loss	$ (865,385)	$ (889,421)	$ (760,277)

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, 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
Exercise of common stock options, net of tax withholdings	2,926	28	189,343	—	—	189,371
Issuance of common stock under equity plans	350	4	11,079	—	—	11,083
Issuance of common stock to strategic partners, net of closing costs	963	10	99,488	—	—	99,498
Stock-based compensation expense related to equity-classified awards	—	—	142,988	—	—	142,988
Other comprehensive loss	—	—	—	(7,104)	—	(7,104)
Net loss	—	—	—	—	(858,281)	(858,281)
Balance as of December 31, 2020	116,427	$ 1,164	$ 5,644,074	$ (43,622)	$ (4,585,369)	$ 1,016,247

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,		
	2020	2019	2018
Cash flows from operating activities:			
Net loss	$ (858,281)	$ (886,116)	$ (761,497)
Non-cash adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	34,772	17,175	15,248
Amortization and interest accretion related to operating leases	39,663	37,193	—
Non-cash interest expense on liability related to the sale of future royalties	84,496	—	—
Stock-based compensation	139,873	174,841	157,752
Realized and unrealized gain on marketable equity securities	(54,042)	(11,288)	(3,564)
Change in fair value of liability obligation	—	(9,422)	—
Gain on litigation settlement	—	—	(10,000)
Other	11,259	(3,191)	(5,654)
Changes in operating assets and liabilities:			
Accounts receivable, net	(56,236)	(24,238)	15,242
Proceeds from landlord lease incentive for tenant improvements	5,550	30,170	25,350
Inventory	(35,426)	(32,411)	(22,645)
Prepaid expenses and other assets	15,230	(22,042)	(35,067)
Accounts payable, accrued expenses and other liabilities	143,732	92,354	74,835
Deferred revenue	(43,965)	392,251	(12,616)
Operating lease liability	(41,586)	(33,703)	—
Net cash used in operating activities	(614,961)	(278,427)	(562,616)
Cash flows from investing activities:			
Purchases of property, plant and equipment	(70,361)	(140,156)	(126,887)
Purchases of marketable securities	(2,025,626)	(2,075,925)	(1,104,046)
Sales and maturities of marketable securities	1,691,669	1,775,404	1,518,703
Proceeds from maturity of restricted investments	—	30,000	—
Purchases of restricted investments	(25,900)	—	(14,825)
Other	(5,300)	(7,000)	—
Net cash (used in) provided by investing activities	(435,518)	(417,677)	272,945
Cash flows from financing activities:			
Proceeds from exercise of stock options and other types of equity, net	200,484	71,284	65,470
Proceeds from the sale of future royalties	500,000	—	—
Proceeds from development derivative	8,400	—	—
Offering proceeds, net of costs	—	381,900	—
Proceeds from issuance of term loan	200,000	—	—
Repayment of term loan	—	(30,000)	—
Proceeds from issuance of common stock to strategic partners, net of closing costs	99,498	400,000	—
Payment of transaction costs related to sale of future royalties and term loan	(13,403)	—	—
Net cash provided by financing activities	994,979	823,184	65,470
Effect of exchange rate changes on cash, cash equivalents and restricted cash	4,918	(83)	—
Net (decrease) increase in cash, cash equivalents and restricted cash	(50,582)	126,997	(224,201)
Cash, cash equivalents and restricted cash, beginning of period	549,628	422,631	646,832
Cash, cash equivalents and restricted cash, end of period	$ 499,046	$ 549,628	$ 422,631
Supplemental disclosure of noncash investing and financing activities:			
Capital expenditures included in accounts payable and accrued expenses	$ 14,518	$ 14,876	$ 33,274
Lease liabilities arising from obtaining right-of-use assets	$ 34,435	$ 4,530	$ —
Receivable and liability related to the sale of future royalties	$ 500,000	$ —	$ —

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 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., and also received marketing authorization for ONPATTRO from the European Commission, or EC. As of December 31, 2020, we have launched ONPATTRO in the U.S., Europe, Japan, Canada and several additional countries. In the fourth quarter of 2019, we received approval for GIVLAARI from the FDA and began commercializing and generating product revenues in the U.S. In 2020, we obtained additional regulatory approval from the EC for GIVLAARI and expanded into European and other markets. In the fourth quarter of 2020, we received regulatory approval from the FDA and EC for OXLUMO and began recording net product revenues subsequent to commercial launch. Regulatory filings in additional markets are pending or planned for 2021 and beyond for each of our commercial products.

In 2020, we entered into a broad strategic financing collaboration with The Blackstone Group Inc. and certain of its affiliates which includes a purchase and sale agreement, a credit agreement, a funding agreement for the clinical development of vutrisiran and ALN-AGT and a stock purchase agreement, under which The Blackstone Group Inc. and certain of its affiliates will provide up to $2.00 billion to support our advancement of innovative RNAi therapeutics. Each executed agreement is a separate unit of account and was recorded at fair value. Please read Note 5, Note 7, Note 8 and Note 13, respectively, for additional information regarding each executed agreement set forth above.

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, we use estimates and assumptions related to our inventory valuation and related reserves, liability related to the sale of future royalties, development derivative liability, 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.

The full extent to which the COVID-19 pandemic will directly or indirectly impact our business, results of operations and financial condition, including sales, expenses, reserves and allowances, the supply of our products and product candidates, clinical trials and research and development costs, will depend on future developments that are highly uncertain, including as a result of new information that may emerge concerning COVID-19 and variants thereof, and the actions taken to contain or treat it or vaccinate against it, as well as the economic impact on local, regional, national and international customers and markets. We have made estimates of the impact of COVID-19 within our financial statements and there may be changes to those estimates in future periods. Actual results may differ from these 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 securities as of December 31, 2020, together with the cash we expect to generate from product sales and under our current alliances, including our strategic financing collaboration with The Blackstone Group Inc. and certain of its affiliates, 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 securities. As of December 31, 2020 and 2019, substantially all of our cash, cash equivalents and marketable 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, 2020, 2019 and 2018, our revenues were generated primarily from product sales to distributors and collaborations with strategic partners. For the years ended December 31, 2020, 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:

	Year Ended December 31,		
	2020	2019	2018
Distributor A	31 %	44 %	13 %
Regeneron Pharmaceuticals	12 %	*	*
Sanofi Genzyme	*	*	58 %
Vir Biotechnology	*	*	16 %

* Represents less than 10%

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

	As of December 31,	
	2020	2019
Distributor A	19 %	28 %
Novartis AG	16 %	*
Distributor B	14 %	10 %
Regeneron Pharmaceuticals	11 %	*
Sanofi Genzyme	*	14 %

* 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 if an impairment loss exists, 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, 2020, 2019 or 2018. 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.

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, 2020 and 2019, based on our estimation of expected write-offs, we determined an allowance for doubtful accounts was not material. 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 and classified based on the anticipation of when it will be consumed either within our normal operating cycle (short-term) or beyond (long-term). 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, 2020, 2019 and 2018, we recorded $30.2 million, $16.6 million and $12.8 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

Leases

Effective January 1, 2019, we adopted Accounting Standards Update, or ASU, 2016-02, Leases Topic 842, or ASC 842, using a modified retrospective basis and utilizing the effective date as the date of initial application.

We determine if an arrangement is a lease at contract inception based on the facts and circumstances present in the arrangement. All our leases are classified as operating leases under the new leasing standard. We record operating lease assets and lease liabilities in our consolidated balance sheets. Operating lease assets represent our right to use an underlying asset for the lease term and operating lease liabilities represent our obligation to make lease payments arising from the leasing arrangement. Operating lease assets and operating lease liabilities are recognized at commencement date based on the present value of lease payments over the lease term. As most of our leases do not provide an implicit rate, in determining the operating lease liabilities, we use an estimate of our incremental borrowing rate based on the information available at commencement. Lease expense for lease payments is recognized on a straight-line basis over the lease term. Short-term leases, or leases that have a lease term of 12 months or less at commencement date, are excluded from this treatment and are recognized on a straight-line basis over the term of the lease.

Clinical 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, 2020 and 2019, we had not capitalized any costs to obtain any of our contracts.

Net Product Revenues

Our net product revenues 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.

We record reserves, based on contractual terms, for 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. The following are the components of variable consideration related to product revenues:

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 within each customer agreement. 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.

Net Revenues from Collaborations

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, Net Revenues from Collaborations. 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 (less than 12 months) or long-term (more than 12 months) deferred revenue based on our best estimate of when 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, amortization of intangible assets associated with the sale of our products and costs related to sales of product supply under our collaboration agreements. 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

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.

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 have recorded no interest and penalty expense related to uncertain tax positions for the years ended December 31, 2020, 2019 or 2018.

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, certain 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, 2020, 2019 and 2018, we charged to research and development expense costs associated with license fees of $2.8 million, $37.0 million and $8.0 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.

Liability Related to the Sale of Future Royalties

We account for the liability related to the sale of future royalties as a debt financing, as we have significant continuing involvement in the generation of the cash flows. Interest on the liability related to the sale of future royalties will be recognized using the effective interest rate method over the life of the related royalty stream.

The liability related to the sale of future royalties and the related interest expense are based on our current estimates of future royalties and commercial milestones expected to be paid over the life of the arrangement, which we determine by using third-party forecasts of inclisiran's global net revenue. We will periodically assess the expected payments and to the extent the amount or timing of our future estimated payments is materially different than our previous estimates, we will account for any such change by adjusting the liability related to the sale of future royalties and prospectively recognizing the related non-cash interest expense.

Development Derivative Liability

Development derivative liability is recorded at fair value based on the probability weighted present value of the estimated cash flows pursuant to contractual terms of the funding agreement. The liability is remeasured quarterly with any change in fair value recorded in other income (expense) on the consolidated statements of operations and comprehensive loss.

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 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:

	As of December 31,		
(In thousands)	**2020**	**2019**	**2018**
Options to purchase common stock	11,692	13,069	12,573
Unvested restricted common stock	1,160	749	36
Total	12,852	13,818	12,609

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, 2020 and 2019, substantially all of our consolidated property, plant and equipment, net was from U.S. operations. For the years ended December 31, 2020, 2019 and 2018, net revenues from collaborations were attributed to the U.S. Please read Note 3 for information regarding our net product sales by geography.

Recently Adopted Accounting Pronouncements

In June 2016, the Financial Accounting Standards Board, or FASB, issued ASU 2016-13 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 and did not have a significant impact on our consolidated financial statements and related disclosures.

In August 2018, the FASB issued ASU 2018-13 amending 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 and did not have a significant impact on our consolidated financial statements and related disclosures.

In August 2018, the FASB issued ASU 2018-15 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 and did not have a significant impact on our consolidated financial statements and related disclosures.

In November 2018, the FASB issued ASU 2018-18 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. This standard did not have a significant impact on our consolidated financial statements and related disclosures.

In December 2019, the FASB issued ASU 2019-12 amending accounting guidance that simplify 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. We early adopted the amendments as of January 1, 2020, on a prospective basis. The amendments did not have a significant impact on our consolidated financial statements and related disclosures.

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. We adopted ASC 606 in the first quarter of 2018 and recognized the cumulative effect of initially applying ASC 606 as an adjustment to opening retained earnings for the year ended December 31, 2018.

3. NET PRODUCT REVENUES

Net product revenues by geography consist of the following:

	Year Ended December 31,		
(In thousands)	2020	2019	2018
ONPATTRO			
United States	$ 151,574	$ 116,302	$ 8,589
Europe	107,755	43,980	3,946
Rest of World (primarily Japan)	46,752	6,105	—
Total	$ 306,081	$ 166,387	$ 12,535
GIVLAARI			
United States	$ 42,797	$ 150	$ —
Europe	12,000	—	—
Rest of World	309	—	—
Total	$ 55,106	$ 150	$ —
OXLUMO			
Europe	$ 333	$ —	$ —
Total net product revenues	$ 361,520	$ 166,537	$ 12,535

As of December 31, 2020 and 2019, net product revenue-related receivables of $68.9 million and $28.1 million, respectively, were included in "Accounts receivable, net."

The following table summarizes balances and activity in each product revenue allowance and reserve category:

	As of December 31, 2020			
(In thousands)	Chargebacks and Rebates	Trade Discounts and Allowances	Returns Reserve and Other Incentives	Total
Beginning balance	$ 32,487	$ 410	$ 1,978	$ 34,875
Provision related to current period sales	103,706	4,650	5,702	114,058
Credit or payments made during the period for current year sales	(42,493)	(4,388)	(2,704)	(49,585)
Credit or payments made during the period for prior year sales	(2,995)	(33)	(1,213)	(4,241)
Total	$ 90,705	$ 639	$ 3,763	$ 95,107

	As of December 31, 2019			
(In thousands)	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 period sales	(109)	(218)	(220)	(547)
Total	$ 32,487	$ 410	$ 1,978	$ 34,875

4. NET REVENUES FROM COLLABORATIONS

The following table summarizes our total consolidated net revenues from collaborations:

	Year Ended December 31,		
(In thousands)	2020	2019	2018
Regeneron Pharmaceuticals	$ 74,072	$ 26,075	$ —
Vir Biotechnology	31,396	12,809	12,778
Novartis AG	22,208	2,315	2,789
Sanofi Genzyme	995	10,976	46,000
Other	2,662	1,038	806
Total	$ 131,333	$ 53,213	$ 62,373

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

	As of December 31,	
(In thousands)	2020	2019
Receivables included in "Accounts receivable, net"	$ 33,542	$ 14,929
Contract liabilities included in "Deferred revenue"	120,021	153,117

We recognized revenue of $54.4 million and $4.0 million in the years ended December 31, 2020 and 2019, respectively, that was included in the contract liability balance at the beginning of the period.

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:

	Year Ended December 31,								
	2020			2019			2018		
(In thousands)	Clinical Trial and Manufacturing	External Services	Other	Clinical Trial and Manufacturing	External Services	Other	Clinical Trial and Manufacturing	External Services	Other
Regeneron	$ 13,302	$ 171	$ 44,360	$ 2,793	$ 344	$ 21,779	$ —	$ —	$ —
Sanofi Genzyme	644	181	2,132	11,505	334	2,017	36,600	5,340	1,279
Vir	18,470	584	11,590	10,353	381	4,745	7,272	8,251	548
Novartis	999	—	700	2,025	—	696	1,664	2	203
Other	—	—	—	—	—	—	—	2,150	1,097
Total	$ 33,415	$ 936	$ 58,782	$ 26,676	$ 1,059	$ 29,237	$ 45,536	$ 15,743	$ 3,127

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 revenues from collaborations. For the years ended December 31, 2020, 2019 and 2018, we did not incur material selling, general and administrative expenses related to our collaboration agreements.

Product Alliances

Regeneron Pharmaceuticals, Inc.

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. 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 2 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. Reimbursement of our share of costs will be recognized as a reduction to research and development expense in the consolidated statements of operations and comprehensive loss. During the year ended December 31, 2020 and 2019, we recognized $5.4 million and $0.0 million, respectively, as a reduction to research and development expense. 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 as of December 31, 2020, the total transaction price was determined to be $531.8 million, a decrease of $23.3 million from December 31, 2019. As of December 31, 2020, the transaction price is comprised of the upfront payment and variable consideration related to development, manufacture and supply activities. 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, is accounted for as collaboration revenue.

The following tables provide 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:

	Transaction Price Allocated	Deferred Revenue		
Performance Obligations	As of December 31, 2020	As of December 31, 2020	As of December 31, 2019	Accounting Guidance
Research Services Obligation	$ 200,600	$ 54,900	$ 84,800	ASC 606
C5 License Obligation	85,200	58,700	65,800	ASC 606
C5 Co-Co Obligation	246,000	231,400	243,000	ASC 808
Total	$ 531,800	$ 345,000	$ 393,600	

	Revenue Recognized During		
Performance Obligations	Year Ended December 31, 2020	Year Ended December 31, 2019	Accounting Guidance
Research Services Obligation	$ 44,800	$ 21,000	ASC 606
C5 License Obligation	7,100	—	ASC 606
C5 Co-Co Obligation	11,700	2,900	ASC 808
	$ 63,600	$ 23,900	

As of December 31, 2020, the aggregate amount of the transaction price allocated to the remaining Research Services Obligation and C5 License Obligation that was unsatisfied was $212.9 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

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 were set at 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 ASC 606 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 ASC 606 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 ASC 606 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 ASC 606 (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 a $51.5 million equity discount related to the stock purchase agreement pursuant to which Sanofi Genzyme purchased 8,766,338 shares of our common stock and paid $700 million in aggregate cash consideration to us. 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.

ASC 606 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 ASC 606, 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 ASC 606. 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 ASC 606.

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. We record royalties payable to Sanofi Genzyme with respect to 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 ASC 606, 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.

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.

Novartis AG

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. We refer to this agreement, as amended through the date hereof, as the MDCO License Agreement. On January 6, 2020, Novartis AG, or Novartis, completed its acquisition of MDCO and assumed all rights and obligations under the MDCO License Agreement. As of December 31, 2020, we have earned $45.0 million of milestones and upon achievement of certain events, we will be entitled to receive additional milestones, up to an aggregate of $135.0 million, including $25.0 million associated with the U.S. regulatory approval milestone, $10.0 million in other specified regulatory milestones and $100.0 million in specified commercialization milestones. In addition, we will be entitled to royalties ranging from 10% up to 20% based on annual worldwide net sales of licensed products by Novartis, its affiliates and sublicensees, subject to reduction under specified circumstances. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments under the MDCO License Agreement.

Under the MDCO License Agreement, we had responsibility for the development of inclisiran until Phase 1 Completion, as defined in the MDCO License 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 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 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 License Agreement. Novartis has the sole right and responsibility to manufacture and supply inclisiran for development and commercialization, subject to the terms of the MDCO License Agreement and the supply and technical transfer agreement.

Unless terminated earlier in accordance with the terms of the agreement, the MDCO License 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 License 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 License 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 License Agreement will expire in the U.S., Europe, China and Japan in 2036 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 License Agreement in the event the other party fails to cure a material breach or upon patent-related challenges by the other party. In addition, Novartis has the right to terminate the agreement without cause at any time upon four months' prior written notice.

During the term of the MDCO License 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 License Agreement.

We evaluated the MDCO License Agreement and concluded that Novartis meets the definition of a customer and that the MDCO License 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 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 Novartis 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 License 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 Novartis. We determined that, pursuant to ASC 606, 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 License Agreement has a single identified or combined performance obligation.

None of the unearned milestones are included in the transaction price, as all unearned milestone amounts are 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. During 2018, we completed the performance obligations identified in the MDCO License Agreement, including the supply and technical transfer agreement, however, we continue to receive additional orders for supply of certain material. We consider such orders as promised goods to be distinct from the other performance obligations since Novartis now has the ability to manufacture on its own through its own vendors. Such option orders will be treated as separate agreements and any associated revenue will be recognized upon transfer of control.

Vir Biotechnology, Inc.

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. In March 2020, we achieved a development milestone relating to ALN-HBV02 and earned a $15.0 million cash milestone and 1,111,111 shares of Vir's common stock, which were received in the second quarter of 2020. In June 2020, we earned and received a $10.0 million payment from Vir related to Vir's sublicense for ALN-HBV02 in China. 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.

In March and April 2020, we entered into amendments to the Vir Agreement to expand our collaboration to include the development and commercialization of RNAi therapeutics targeting SARS-CoV-2, the virus that causes the disease COVID-19, along with three additional targets focused on human host factors for SARS-CoV-2, including angiotensin converting enzyme-2 and transmembrane protease, serine 2 and potentially a third mutually selected host factor target. Under the Vir amendments, we and Vir were each responsible for our own pre-clinical development costs incurred in performing our allocated responsibilities under an agreed-upon initial pre-clinical development plan. Under the original agreements, we and Vir agreed to equally share certain costs incurred in connection with the manufacture of non-GMP drug product required for pre-clinical development prior to filing an IND for the first product in the coronavirus program. We also agreed that Vir would lead all development and commercialization of any selected development candidates.

In December 2020, we signed a letter agreement to amend the Vir Agreement such that we are solely responsible for conducting pre-clinical research activities under the pre-clinical development plan, related to the COVID-19 activities in the March and April 2020 amendments, at our discretion and sole expense and effective as of July 1, 2020, we are responsible for all pre-clinical development costs incurred under such plan for such COVID-19 related activities.

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.

We identified one performance obligation under the Vir Agreement, as amended, comprised of: i) the exclusive license to develop, manufacture and commercialize RNAi therapeutics (including ALN-HBV02); ii) the obligation to deliver four additional development candidates and supply product for each such RNAi therapeutic program; and iii) the obligation to deliver up to four development candidates and supply product for RNAi therapeutic programs targeting SARS-CoV-2. The license is not distinct from the services, including the obligation to deliver development candidates and supply product, as Vir cannot benefit on its own from the value of the license without receipt of such services and supply. We measure proportional performance over time using an input method based on cost incurred relative to the total estimated costs for the identified performance obligation, 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 total transaction price. 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. As of December 31, 2020, the total transaction price was determined to be $110.1 million, an increase of $72.4 million from December 31, 2019 as a result of additional cash and shares received from Vir in 2020, as well as an increase in our estimated variable consideration. As of December 31, 2020, the transaction price is comprised of the upfront payment, fair value of non-cash equity consideration at contract inception, milestones achieved, and variable consideration related to development, manufacture and supply activities. We utilized the expected value method to determine the amount of reimbursement for these activities. The total transaction price is allocated entirely to the single performance obligation. We determined any variable consideration related to sales-based royalties and milestones related to the exclusive license to be constrained and therefore excluded such consideration from the transaction price.

As of December 31, 2020, the aggregate amount of the transaction price allocated to the performance obligation that was unsatisfied was $51.7 million, which is expected to be recognized through the term of the Vir Agreement as the services are performed.

5. LIABILITY RELATED TO THE SALE OF FUTURE ROYALTIES

On April 10, 2020, we entered into a purchase and sale agreement, or Purchase Agreement, with BX Bodyguard Royalties L.P. (an affiliate of The Blackstone Group Inc.), or Blackstone Royalties, under which Blackstone Royalties acquired 50% of royalties payable, or Royalty Interest, with respect to net sales by MDCO, its affiliates or sublicensees of inclisiran and any other licensed products under the MDCO License Agreement, and 75% of the commercial milestone payments payable under the MDCO License Agreement, together with the Royalty Interest, referred to as the Purchased Interest. If Blackstone Royalties does not receive payments in respect of the Royalty Interest by December 31, 2029, equaling at least $1.00 billion, Blackstone Royalties will receive 55% of the Royalty Interest beginning on January 1, 2030. In consideration for the sale of the Purchased Interest, Blackstone Royalties paid us $500.0 million in April 2020 and has an unconditional obligation to pay us an additional $500.0 million on September 30, 2021, which was recorded as a receivable upon execution of the Purchase Agreement.

We continue to own or control all inclisiran intellectual property rights and are responsible for certain ongoing manufacturing and supply obligations related to the generation of the Purchased Interest. Due to our continuing involvement, we will continue to account for any royalties and commercial milestones due to us under the MDCO License Agreement as revenue on our consolidated statement of operations and comprehensive loss and record the proceeds from this transaction as a liability, net of closing costs, on our consolidated balance sheet.

In order to determine the amortization of the liability related to the sale of future royalties, we are required to estimate the total amount of future payments to Blackstone Royalties over the life of the Purchase Agreement. The $1.00 billion liability, recorded at execution of the agreement, will be accreted to the total of these royalty and commercial milestone payments as interest expense over the life of the Purchase Agreement. At execution and as of December 31, 2020, our estimate of this total interest expense resulted in an effective annual interest rate of 11%. This estimate contains assumptions that impact both the amount recorded at execution and the interest expense that will be recognized in future periods.

As payments are made to Blackstone Royalties, the balance of the liability will be effectively repaid over the life of the Purchase Agreement. The exact timing and amount of repayment is likely to change each reporting period. A significant increase or decrease in net sales of inclisiran will materially impact the liability related to the sale of future royalties, interest expense and the time period for repayment. We will periodically assess the expected payments to Blackstone Royalties and to the extent the amount or timing of such payments is materially different than our initial estimates, we will prospectively adjust the amortization of the liability related to the sale of future royalties and the related interest expense.

As of December 31, 2020, the carrying value of the liability related to the sale of future royalties was $1.07 billion, net of closing costs of $13.0 million. The carrying value of the liability related to the sale of future royalties approximates fair value as of December 31, 2020 and is based on our current estimates of future royalties and commercial milestones expected to be paid to Blackstone Royalties over the life of the arrangement, which are considered Level 3 inputs. For the year ended December 31, 2020, we recognized interest expense of $84.5 million.

The following table shows the activity with respect to the liability related to the sale of future royalties, in thousands:

Liability related to the sale of future royalties as of April 10, 2020	$	1,000,000
Capitalized closing costs		(12,955)
Interest expense recognized		84,496
Carrying value of liability related to sale of future royalties as of December 31, 2020	$	1,071,541

6. OTHER BALANCE SHEET DETAILS

Inventory

The components of inventory are summarized as follows:

	As of December 31,	
(In thousands)	2020	2019
Raw materials	$ 63,460	$ 15,418
Work in process	16,149	38,275
Finished goods	12,693	2,655
Total inventory	$ 92,302	$ 56,348

As of December 31, 2020, we had long-term inventory of $17.1 million in other assets in our consolidated balance sheet as we anticipate such inventory being consumed beyond our normal operating cycle. As of December 31, 2019, we had no long-term inventory. As of December 31, 2020 and 2019, there was no capitalized inventory for products awaiting regulatory approval.

Property, Plant and Equipment, Net

Property, plant and equipment, net consist of the following:

	As of December 31,	
(In thousands)	**2020**	**2019**
Buildings	$ 262,637	$ 250,380
Leasehold improvements	149,505	132,632
Laboratory equipment	48,930	29,755
Manufacturing equipment	41,089	—
Construction in progress	28,005	54,195
Computer equipment and software	19,064	14,956
Furniture and fixtures	11,066	10,339
Land	9,080	9,080
	569,376	501,337
Less: accumulated depreciation	(104,347)	(76,158)
Total	$ 465,029	$ 425,179

Accrued Expenses

Accrued expenses consist of the following:

	As of December 31,	
(In thousands)	**2020**	**2019**
Compensation and related	$ 97,433	$ 68,304
Product rebates and discounts	94,242	32,670
Pre-clinical, clinical trial and manufacturing	46,506	34,269
Contingent liabilities	41,216	—
Licensing and collaboration agreements	15,424	20,622
Consulting and professional services	11,501	14,251
Other	49,587	27,085
Total	$ 355,909	$ 197,201

Cash, Cash Equivalents and Restricted Cash

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:

	As of December 31,		
(In thousands)	**2020**	**2019**	**2018**
Cash and cash equivalents	$ 496,580	$ 547,178	$ 420,146
Total restricted cash included in prepaid expenses, other current assets and long-term other assets	2,466	2,450	2,485
Total cash, cash equivalents, and restricted cash shown in the consolidated statements of cash flows	$ 499,046	$ 549,628	$ 422,631

Accumulated Other Comprehensive (Loss) Income

The following table summarizes the changes in accumulated other comprehensive (loss) income, by component:

(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, 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)
Other comprehensive (loss) income before reclassifications	—	(531)	(14)	(7,081)	(7,626)
Amounts reclassified from other comprehensive income	—	297	225	—	522
Net other comprehensive (loss) income	—	(234)	211	(7,081)	(7,104)
Balance as of December 31, 2020	$ (32,792)	$ (3,754)	$ 348	$ (7,424)	$ (43,622)

7. CREDIT AGREEMENT

On April 10, 2020, we entered into a credit agreement, or Credit Agreement, among us, certain of our subsidiaries (such subsidiaries, together with us, the Loan Parties), funds or accounts managed or advised by GSO Capital Partners LP (now Blackstone Alternative Credit Advisors LP) and certain other affiliates of The Blackstone Group Inc., and the other lenders from time to time parties thereto, collectively, the Lenders, and Wilmington Trust, National Association, as the administrative agent for the Lenders. The Credit Agreement provides for a senior secured delayed draw term loan facility, referred to as the Term Loans, which consists of three tranches providing funding up to $700.0 million. The Tranche 1 Loan of $200.0 million was drawn as of December 31, 2020 and is included in long-term debt in the consolidated balance sheets. The remaining two tranches will provide funds as follows:

Tranche	Requested No Later Than	Aggregate Principal Amount, up to (in thousands)
Tranche 2 Loan	June 30, 2021	$ 250,000
Tranche 3 Loan	December 31, 2021	$ 250,000

In addition, we may (a) at any time following April 10, 2021, request an increase in respect of the unfunded commitments in an amount not to exceed $50.0 million on terms to be agreed and subject to the consent of the Lenders providing such increase and/or (b) at any time prior to April 10, 2021, cancel the unfunded commitments or reallocate the unfunded commitments in respect of the Tranche 2 Loan or Tranche 3 Loan to the Tranche 1 Loan and/or the Tranche 2 Loan in an amount not to exceed $100.0 million in the aggregate for all such cancellations or reallocations.

The Tranche 2 Loan will be requested no later than June 30, 2021 and the Tranche 3 Loan will be requested no later than December 31, 2021, in each case, subject to customary terms and conditions, including, in the case of the Tranche 2 Loan and Tranche 3 Loan, either (a) the first sale of inclisiran in the U.S. for end use or consumption after FDA regulatory approval thereof or (b) revenue attributable to ONPATTRO and GIVLAARI equal to or greater than $300.0 million as of the last day of the most recently ended twelve month period, referred to as the Subsequent Borrowing Conditions. As of December 31, 2020, the Subsequent Borrowing Conditions have been satisfied. The Term Loans mature in December 2027. We can elect an interest rate of either LIBOR plus 7%, subject to a floor of 1%, referred to as the LIBOR Rate, or a base rate plus 6%, subject to a floor of 2%. We may, at our option, pay interest in kind on interest due through 2023 at a rate that is 1% higher than the interest rate otherwise applicable to such Term Loan. We drew the Tranche 1 Loan in December 2020, elected a LIBOR Rate plus 7%, and paid a $5.0 million funding fee. On the date the Tranche 2 Loan or Tranche 3 Loan is funded, we will pay a funding fee equal to 2.5% of the principal amount of the Term Loans funded on such date. In addition, we will pay an exit fee equal to 1% of the

commitments in respect of the Term Loans, payable upon any repayment of the Term Loans or termination of the unfunded Term Loan commitments. As of December 31, 2020, our interest rate was 8%.

We are obligated to pay interest due on the Term Loans from 2021 to 2022 which will be calculated without regard to the Term Loans being prepaid or an unfunded tranche being terminated during this period (in whole or in part). Any prepayments of Term Loans or terminations of unfunded tranches that occur between 2023 and 2025 are subject to a fee of up to 5% of the loan principal that is prepaid or the amount of the unfunded tranche that is terminated.

All obligations under the Credit Agreement are secured, subject to certain exceptions, by security interests in the following assets: (1) intellectual property owned by us relating to ONPATTRO, GIVLAARI and vutrisiran, (2) the equity interests held by the Loan Parties in their subsidiaries, (3) all of our ownership of the inclisiran royalty remaining after the royalty purchase under the Purchase Agreement, and (4) material real property, and certain personal property, including, without limitation, cash held in certain deposit accounts of the Loan Parties and equipment.

The Credit Agreement contains negative covenants that, among other things and subject to certain exceptions, could restrict our ability to, incur additional liens, incur additional indebtedness, make investments, including acquisitions, engage in fundamental changes, sell or dispose of assets that constitute collateral, including certain intellectual property, pay dividends or make any distribution or payment on or redeem, retire or purchase any equity interests, amend, modify or waive certain material agreements or organizational documents and make payments of certain subordinated indebtedness. Additionally, the Credit Agreement contains certain customary representations and warranties, affirmative covenants and provisions relating to events of default, including nonpayment of principal, interest and other amounts; failure to comply with covenants; the rendering of judgments or orders or default by us in respect of other material indebtedness; and certain insolvency and ERISA events. The Credit Agreement also requires us to have consolidated liquidity of at least $100.0 million as of the last day of each fiscal quarter. As of December 31, 2020, we were in compliance with the applicable terms and conditions of the covenants under the Credit Agreement.

8. DEVELOPMENT DERIVATIVE LIABILITY

On August 15, 2020, we entered into a co-development agreement, referred to as the Funding Agreement, with BXLS V Bodyguard – PCP L.P. and BXLS Family Investment Partnership V – ESC L.P., collectively referred to as Blackstone Life Sciences, pursuant to which Blackstone Life Sciences will provide up to $150.0 million in funding for the clinical development of vutrisiran and ALN-AGT, two of our cardiometabolic programs. With respect to vutrisiran, Blackstone Life Sciences has committed to provide up to $70.0 million to fund development costs related to the HELIOS-B Phase 3 clinical trial. In addition, Blackstone Life Sciences has the right, but is not obligated, to fund up to $26.0 million for development costs related to a Phase 2 clinical trial of ALN-AGT and up to $54.0 million for development costs related to a Phase 3 clinical trial of ALN-AGT. The amount of funding ultimately provided by Blackstone Life Sciences is dependent on us achieving specified development milestones with respect to each clinical trial. We retain sole responsibility for the development and commercialization of both vutrisiran and ALN-AGT.

As consideration for Blackstone Life Sciences' funding for vutrisiran clinical development costs, we have agreed to pay Blackstone Life Sciences a 1% royalty on net sales of vutrisiran for a 10-year term beginning upon the first commercial sale following regulatory approval of vutrisiran for ATTR-cardiomyopathy, as well as fixed payments of up to 2.5 times their investment over a two-year period upon regulatory approval of vutrisiran for ATTR-cardiomyopathy in specified countries, unless it is later withdrawn from the market following a mandatory recall. As consideration for Blackstone Life Sciences' funding for Phase 2 clinical development costs of ALN-AGT, we have agreed to pay Blackstone Life Sciences fixed payments of up to 3.25 times their Phase 2 investment over a four-year period upon the successful completion of the ALN-AGT Phase 2 clinical trial, unless certain regulatory events affecting the continued development of ALN-AGT occur. As consideration for Blackstone Life Sciences' funding for Phase 3 clinical development costs of ALN-AGT, we have agreed to pay Blackstone Life Sciences fixed payments of up to 4.5 times their Phase 3 investment over a four-year period upon regulatory approval of ALN-AGT in specified countries, unless it is later withdrawn from the market following a mandatory recall.

Our payment obligations under the Funding Agreement will be secured, subject to certain exceptions, by security interests in intellectual property owned by us relating to vutrisiran and ALN-AGT, as well as in our bank account in which the funding deposits will be made.

We and Blackstone Life Sciences each have the right to terminate the Funding Agreement in its entirety in the event of the other party's bankruptcy or similar proceedings. We and Blackstone Life Sciences may each terminate the Funding Agreement in its entirety or with respect to either product in the event of an uncured material breach by the other party, or with respect to a product for certain patient health and safety reasons, or if regulatory approval in specified major market countries is not obtained for the product following the completion of clinical trials for the product. In addition, Blackstone Life Sciences has the right to terminate the Funding Agreement in its entirety upon the occurrence of certain events affecting our ability to make payments under the agreement or to develop or commercialize the products, or upon a change of control of us. Blackstone Life Sciences may also terminate the Funding Agreement with respect to a product if the joint steering committee elects to terminate

the development program for that product in its entirety, if certain clinical endpoints are not achieved for that product or, with respect to vutrisiran only, if our right to develop or commercialize vutrisiran is enjoined in a specified major market as a result of an alleged patent infringement. In certain termination circumstances, we will be obligated to pay Blackstone Life Sciences an amount that is equal to, or a multiplier of, the development funding received from Blackstone Life Sciences, and we may remain obligated under certain circumstances to make the payments to Blackstone Life Sciences described above, or the royalty described above in the case of vutrisiran, should we obtain regulatory approval for vutrisiran or ALN-AGT following termination.

We account for the Funding Agreement under ASC 815 as a derivative liability, measured at fair value, within other liabilities on our consolidated balance sheets. The liability was initially recorded at $4.2 million upon receipt of funding in the third quarter of 2020, pursuant to the contractual terms, and then subsequently increased in the fourth quarter of 2020 upon receipt of additional funding. The change in fair value due to the remeasurement of the development derivative liability resulted in a $17.2 million loss for the year ended December 31, 2020, recorded within other income, net on our consolidated statements of operations and comprehensive loss.

As of December 31, 2020, the derivative liability is classified as a Level 3 financial liability in the fair value hierarchy. The valuation method incorporates certain unobservable Level 3 key inputs including (i) the probability and timing of achieving stated development milestones to receive payments from Blackstone Life Sciences, (ii) the probability and timing of achieving regulatory approval and payments to Blackstone Life Sciences, (iii) an estimate of the amount and timing of the royalty payable on net sales of vutrisiran, assuming regulatory approval, (iv) our cost of borrowing (15%), and (v) Blackstone Life Sciences' cost of borrowing (4%).

The following table presents the activity with respect to the development derivative liability, in thousands:

Development derivative liability as of August 15, 2020	$ —
Amount received under the Funding Agreement	8,400
Loss recorded from remeasurement of development derivative liability	17,185
Development derivative liability as of December 31, 2020	$ 25,585

9. FAIR VALUE MEASUREMENTS

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

(In thousands)	As of December 31, 2020	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial assets				
Cash equivalents:				
U.S. treasury securities	$ 20,000	$ —	$ 20,000	$ —
Money market funds	75,726	75,726	—	—
Marketable debt securities:				
U.S. government-sponsored enterprise securities	245,214	—	245,214	—
U.S. treasury securities	1,087,968	—	1,087,968	—
Marketable equity securities	44,633	44,633	—	—
Restricted cash (money market funds)	1,483	1,483	—	—
Total financial assets	$ 1,475,024	$ 121,842	$ 1,353,182	$ —
Financial liabilities				
Development derivative liability	$ 25,585	$ —	$ —	$ 25,585

(In thousands)	As of December 31, 2019	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial assets				
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 financial assets	$ 1,450,480	$ 135,331	$ 1,315,149	$ —

For the year ended December 31, 2019, there were no transfers between Level 1 and Level 2 financial assets. During the year ended December 31, 2020, we transferred one financial asset from Level 2 to Level 1 as a result of the expiration of a securities' holding restriction on a marketable equity security. There were no other transfers between Level 1 and Level 2 financial assets or liabilities during the year ended December 31, 2020. 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 carrying amount of our debt as of December 31, 2020 approximates fair value as the debt was drawn on December 31, 2020 and has a variable interest rate.

10. MARKETABLE DEBT SECURITIES

The following tables summarize our marketable debt securities:

	As of December 31, 2020			
(In thousands)	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. government-sponsored enterprise securities	$ 245,113	$ 135	$ (34)	$ 245,214
U.S. treasury securities	1,107,721	328	(81)	1,107,968
Total	$ 1,352,834	$ 463	$ (115)	$ 1,353,182

	As of December 31, 2019			
(In thousands)	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

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

(In thousands)	December 31, 2020	December 31, 2019
Cash and cash equivalents	$ 20,000	$ 340,132
Marketable debt securities	1,333,182	975,017
Total	$ 1,353,182	$ 1,315,149

11. 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 for our corporate headquarters from BMR-675 West Kendall Street, LLC, or BMR, under a non-cancelable real property lease. 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, 2020.

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, 2020.

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, 2020.

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, as amended in September 2020, that will expire in March 2024 and June 2026, 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, 2020.

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 all of our real property leases was $50.7 million, $52.4 million and $40.6 million for the years ended December 31, 2020, 2019 and 2018, respectively.

The following table summarizes our costs included in operating expenses related to right of use lease assets we have entered into through December 31, 2020:

(In thousands)	Year Ended December 31, 2020	Year Ended December 31, 2019
Operating lease cost	$ 42,271	$ 38,613
Variable lease cost	11,049	15,209
Total	$ 53,320	$ 53,822

Short-term lease costs were not material for the years ended December 31, 2020 and 2019.

Net cash paid for the amounts included in the measurement of the operating lease liability in our consolidated balance sheet and included in change in operating lease liability within operating activities in our consolidated statement of cash flow was $38.0 million and $33.7 million for the years ended December 31, 2020 and 2019, respectively. The weighted-average remaining lease term and weighted-average discount rate for all leases as of December 31, 2020 was 12 years and 8%, respectively, and as of December 31, 2019 was 13 years and 8%, 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, 2020 were as follows, in thousands:

Year Ending December 31		
2021	$	38,593
2022		46,392
2023		43,764
2024		42,918
2025		41,190
2026 and thereafter		323,473
Total undiscounted lease liability		536,330
Less imputed interest		(206,419)
Total discounted lease liability	$	329,911
Current operating lease liability	$	36,872
Non-current operating lease liability		293,039
Total	$	329,911

12. 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, 2020, 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 Pharmaceuticals, Inc., or 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 are immaterial in connection with our various collaboration 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, 2020, such contingencies have not been recorded in our consolidated financial statements.

Litigation

From time to time, we may be a party to litigation, arbitration or other 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 products or 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 or breach our license or other agreements with such third parties. 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.

Ionis Arbitration

In June 2018, Ionis claimed it was owed payments under our second amended and restated strategic collaboration and license agreement as a result of the January 2018 restructuring of our Sanofi Genzyme collaboration and the related Exclusive TTR License and AT3 License Terms described above. We disputed this and in November 2018, Ionis filed a Demand for Arbitration with the American Arbitration Association against us. The hearing portion of the arbitration process was completed in June 2020, and in October 2020, a partial award was issued by the arbitration panel seeking additional information from us. The arbitration panel issued its final award in December 2020 and required us to pay $41.2 million to Ionis. For the year ended December 31, 2020, we increased our contingent liability related to our arbitration with Ionis by $38.2 million due to the issuance of this final award, and in January 2021 we paid $41.2 million to Ionis.

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 named as defendants certain of our other executive officers, and purported to be brought on behalf of a class of persons who acquired our securities between September 20, 2017 and September 12, 2018 and sought 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 alleged, among other things, that the defendants made materially false and misleading statements related to the efficacy and safety of our product, ONPATTRO. The plaintiff sought, 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. On March 23, 2020, the Court granted our motion and dismissed the Complaint without prejudice. Pursuant to a prior Order of the Court, on June 1, 2020, plaintiff filed a motion seeking leave to file a further amended complaint. We opposed the motion which was fully briefed on June 22, 2020, and remains pending with the Court.

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. On November 2, 2020, the Court entered a Decision and Order denying defendants' motion to dismiss. Defendants filed a notice of appeal of that decision on November 12, 2020, and filed their opening appellate brief on January 4, 2021. Plaintiff's responsive appellate brief is due to be filed on or before March 3, 2021.

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.

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, 2020 or 2019.

13. 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, 2020 and 2019, there were no shares of preferred stock outstanding.

Blackstone Equity Placement

In April 2020, we entered into a stock purchase agreement, or Investors SPA, with certain affiliates of The Blackstone Group Inc., or Investors, pursuant to which we sold 963,486 shares of our common stock to the Investors for aggregate cash consideration of $100.0 million, or $103.79 per share, as part of the broad strategic financing collaboration with The Blackstone Group Inc. The Investors SPA contains customary representations, warranties, and covenants of each of the parties thereto.

Regeneron Equity Placement

In April 2019, we executed a stock purchase agreement, or 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.

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 $400.0 million of equity under the Regeneron SPA would instead have been issued in the form of 1,481,482 shares of our Series A redeemable convertible preferred stock, par value $0.01 per share, at a purchase price of $270.00 per share, that would have converted automatically into common stock on a 1-for-3 basis upon stockholder approval of additional authorized shares of common 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 comprehensive loss during the year ended December 31, 2019, with the offsetting adjustment to equity netting against the $400.0 million proceeds that were received upon closing.

Public Offering

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.

14. 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, pursuant to which 15,480,000 shares of common stock were authorized for issuance. In May 2020, our stockholders approved a second amendment to the 2018 Stock Incentive Plan, as amended, or the Amended 2018 Plan, to increase the number of shares authorized for issuance thereunder by 7,000,000 shares. The Amended 2018 Plan provides for the

granting of stock options, restricted stock and restricted stock units (together, restricted stock awards), stock appreciation rights and other stock-based awards, and has a fungible share pool. Any award that is not a full value award is counted against the authorized share limits specified as one share for each share of common stock subject to the award, and all full value awards, defined as restricted stock awards or other stock-based awards, are counted as one and a half shares for each one share of common stock subject to such full value award.

As of December 31, 2020, an aggregate of 23,035,819 shares of common stock were reserved for issuance under our stock plans, including outstanding stock options to purchase 11,692,209 shares of common stock, 1,160,427 outstanding restricted stock units, 9,223,025 of common stock available for additional equity awards and 960,158 shares available for future grant under our Amended and Restated 2004 Employee Stock Purchase Plan, as amended, 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.

Stock-Based Compensation

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

	Year Ended December 31,		
(In thousands)	**2020**	**2019**	**2018**
Research and development	$ 60,464	$ 88,930	$ 80,509
Selling, general and administrative	79,409	85,911	77,243
Total	$ 139,873	$ 174,841	$ 157,752

The following table summarizes stock-based compensation expense:

	Year Ended December 31,		
(In thousands)	**2020**	**2019**	**2018**
Stock-based compensation expense by type of award:			
Time-based stock options	$ 112,971	$ 99,097	$ 83,403
Performance-based stock options	6,340	48,207	56,419
Time-based restricted stock units	6,909	2,351	538
Performance-based restricted stock units	11,162	22,123	13,144
Other equity programs	3,062	6,466	5,672
Less: Stock-based compensation expense capitalized to inventory	(571)	(3,403)	(1,424)
Total	$ 139,873	$ 174,841	$ 157,752

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

	As of December 31, 2020	
	Unrecognized Expense, Net of Estimated Forfeitures (in thousands)	**Weighted-average Recognition Period (in years)**
Type of award:		
Time-based stock options	$ 183,700	2.44
Time-based restricted stock units	1,593	0.2
Performance-based restricted stock units	1,286	*
Other equity programs	8,159	2.57

* 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 employee stock options granted:

	Year Ended December 31,		
	2020	2019	2018
Risk-free interest rate	0.3 - 1.7%	1.4 - 2.6%	2.7 - 2.9%
Expected dividend yield	—	—	—
Expected option life	5.4 - 7.2 years	5.6 - 7.3 years	5.7 - 7.2 years
Expected volatility	61 - 63%	63 - 66%	64 - 67%

Stock Option Activity

The following table summarizes the activity of our stock option plans, 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 as of December 31, 2019	10,878	$ 76.92		
Granted	2,086	119.96		
Exercised	(2,390)	63.34		
Cancelled	(506)	94.53		
Outstanding as of December 31, 2020	10,068	$ 88.18	6.56	$ 423,864
Exercisable as of December 31, 2020	5,835	$ 76.79	5.19	$ 310,933
Vested or expected to vest as of December 31, 2020	9,692	$ 87.53	6.48	$ 414,208

The weighted-average fair value of stock options granted was $66.28, $49.27 and $66.49 per share for the years ended December 31, 2020, 2019 and 2018, respectively. The intrinsic value of stock options exercised was $177.8 million, $55.4 million and $87.1 million for the years ended December 31, 2020, 2019 and 2018, 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 people, culture and compensation committee.

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

	Number of Options (in thousands)	Weighted-average Exercise Price	Weighted-average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2019	2,191	$ 86.77		
Granted	—	—		
Exercised	(538)	71.28		
Cancelled	(28)	118.62		
Outstanding as of December 31, 2020	1,625	$ 91.35	5.14	$ 62,740
Exercisable as of December 31, 2020	1,414	$ 87.22	4.88	$ 60,458

During the years ended December 31, 2020, 2019 and 2018, there were 0, 889,896 and 763,982 performance-based stock options that vested, respectively. The intrinsic value of performance-based stock options exercised was $34.1 million, $11.0 million and $8.0 million for the years ended December 31, 2020, 2019 and 2018, 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 restricted stock units:

	Number of Units (in thousands)	Weighted-average Grant Date Fair Value
Outstanding as of December 31, 2019	127	$ 77.23
Awarded	17	134.34
Released	(16)	92.97
Cancelled	(11)	76.98
Outstanding as of December 31, 2020	117	$ 83.66

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 as of December 31, 2019	623	$ 85.36
Awarded	715	119.11
Released	(206)	85.67
Cancelled	(89)	99.08
Outstanding as of December 31, 2020	1,043	$ 107.26

The performance-based restricted stock units granted in 2020 and 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 people, culture and compensation committee.

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. In May 2020 our stockholders approved an amendment to the Amended and Restated ESPP, to further increase the number of shares authorized for issuance thereunder from 1,215,789 shares to 1,965,789 shares. Under the Amended and Restated ESPP, as amended, 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 129,394, 109,590 and 78,085 shares during the years ended December 31, 2020, 2019 and 2018, respectively, and as of December 31, 2020, we had 960,158 shares available for issuance under the Amended and Restated ESPP, as amended.

We estimate the fair value of shares to be issued under the Amended and Restated ESPP, as amended, using the Black-Scholes option-pricing model on the date of grant, or first day of the offering period, using the same methodology approach as the employee stock option grants. The following table summarizes the Black-Scholes valuation assumption inputs for stock purchase rights granted under the employee stock purchase plan:

	Year Ended December 31,		
	2020	2019	2018
Risk-free interest rate	0.1% - 0.1%	1.6% - 2.4%	2.0% - 2.5%
Expected dividend yield	—	—	—
Expected option life	6 months	6 months	6 months
Expected volatility	40% - 50%	37% - 56%	47% - 49%

15. INCOME TAXES

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

(In thousands)	2020	2019	2018
Domestic	$ (682,859)	$ (597,602)	$ (573,245)
Foreign	(172,741)	(287,651)	(187,429)
Loss before income taxes	$ (855,600)	$ (885,253)	$ (760,674)

The provision for income taxes consisted of the following:

	Year Ended December 31,		
(In thousands)	2020	2019	2018
Current provision:			
Domestic	$ 61	$ (394)	$ —
Foreign	5,837	3,232	1,611
Total current provision	5,898	2,838	1,611
Deferred benefit:			
Domestic	393	394	(788)
Foreign	(3,610)	(2,369)	—
Total deferred benefit	(3,217)	(1,975)	(788)
Total provision for income taxes	$ 2,681	$ 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 are as follows:

	As of December 31,	
(In thousands)	2020	2019
Deferred tax assets:		
Net operating loss carryforwards	$ 537,382	$ 627,466
Research and development and ODC credits	301,792	261,616
Sale of future royalties	259,014	—
Lease liability	70,402	69,334
Deferred revenue	84,946	—
Deferred compensation	67,530	75,058
Intangible assets	148,168	66,615
Other	32,725	13,660
Total deferred tax assets	1,501,959	1,113,749
Deferred tax liabilities:		
Property, plant and equipment, net	(10,812)	(10,077)
Unrealized gain on marketable securities	(12,766)	(3,932)
Right of use assets	(50,323)	(50,294)
Deferred revenue tax accounting method change	(71,812)	—
Deferred tax asset valuation allowance	(1,349,729)	(1,046,013)
Net deferred tax asset	$ 6,517	$ 3,433

Our effective income tax rate differs from the statutory federal income tax rate, as follows:

	Year Ended December 31,		
(In thousands)	2020	2019	2018
At U.S. federal statutory rate	21.0 %	21.0 %	21.0 %
State taxes, net of federal effect	4.5	3.6	2.1
Stock-based compensation	2.2	—	0.8
Tax credits	3.3	3.7	4.2
Other permanent items	(1.5)	(0.3)	(0.3)
Foreign rate differential	(3.5)	(6.9)	(5.3)
Internal reorganization of certain intellectual property rights	12.3	—	—
Revaluation of deferred credits due to rate change	—	—	(3.5)
Other	(2.7)	(0.1)	—
Valuation allowance	(35.9)	(21.0)	(19.0)
Effective income tax rate	(0.3)%	— %	— %

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. 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 $303.7 million, $185.9 million and $171.8 million for the years ended December 31, 2020, 2019 and 2018, respectively, primarily due to the liability related to the sale of future royalties for the year ended December 31, 2020 and additional net operating losses for the years ended December 31, 2019 and 2018.

During the year ended December 31, 2020, we recorded a net provision for income taxes of $2.7 million. This is primarily comprised of $5.8 million of foreign current provision offset by $3.6 million of deferred provision, primarily related to foreign jurisdictions.

As of December 31, 2020, we had federal and state net operating loss carryforwards of $2.0 billion and $1.9 billion, respectively, to reduce future taxable income. As of December 31, 2020, approximately $0.9 billion of our federal net operating loss carryforward can be carried forward indefinitely while the remaining federal net operating loss of $1.1 billion expires at various dates through 2037. As of December 31, 2020, we had federal and state research and development, including Orphan Drug, and state investment tax credit carryforwards of $272.5 million and $43.1 million, respectively, available to reduce future tax liabilities that expire at various dates through 2040. We have a valuation allowance against the net operating loss and credit carryforwards 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, 2020. 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 income 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. We recognize potential interest and penalties related to unrecognized tax benefits in our provision for income taxes. Our reserve related to income taxes, including potential interest and penalties, was not material as of December 31, 2020 and 2019.

Our uncertain income tax positions do not impact our effective tax rate due to our full valuation allowance in the U.S.

As of December 31, 2020, the unremitted earnings of our foreign subsidiaries are not material. We have not provided for U.S. income taxes or foreign withholding taxes on these earnings as it is our current intention to permanently reinvest these earnings outside the U.S. The tax liability on these earnings is also not material. Events that could trigger a tax liability include, but are not limited to, distributions, reorganizations or restructurings and/or tax law changes.

The tax years 2017 through 2020 remain open to examination by major taxing jurisdictions, which are primarily in the U.S., although net operating loss and credit carryforwards generated prior to 2017 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.

16. 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 $5.2 million and $4.3 million as of December 31, 2020 and 2019, respectively, and is recorded in other liabilities on the consolidated balance sheet. The total net periodic benefit cost for the years ended December 31, 2020, 2019 and 2018 were not material.

17. QUARTERLY FINANCIAL DATA (UNAUDITED)

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

	Three Months Ended			
	March 31, 2020	June 30, 2020	September 30, 2020	December 31, 2020
	(In thousands, except per share data)			
Total revenues	$ 99,476	$ 103,962	$ 125,853	$ 163,562
Operating costs and expenses	309,634	302,821	351,052	357,784
Net loss	$ (182,221)	$ (179,229)	$ (253,291)	$ (243,540)
Net loss per common share — basic and diluted	$ (1.62)	$ (1.56)	$ (2.18)	$ (2.09)
Weighted-average common shares — basic and diluted	112,748	114,911	115,986	116,274

	Three Months Ended			
	March 31, 2019	June 30, 2019	September 30, 2019	December 31, 2019
	(In thousands, except per share data)			
Total 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

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, 2020. 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, 2020, 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, 2020. 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, 2020, 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, 2020 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report, which is included herein.

Changes in Internal Control

There were no changes in our internal control over financial reporting during the quarter ended December 31, 2020 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 2021 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 2021 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 2021 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 2021 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this annual report on Form 10-K relates.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

Incorporated by reference from the information in our Proxy Statement for our 2021 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:"

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Report of Independent Registered Public Accounting Firm	88
Consolidated Balance Sheets as of December 31, 2020 and 2019	90
Consolidated Statements of Operations and Comprehensive Loss for the Years Ended December 31, 2020, 2019 and 2018	91
Consolidated Statements of Stockholders' Equity for the Years Ended December 31, 2020, 2019 and 2018	92
Consolidated Statements of Cash Flows for the Years Ended December 31, 2020, 2019 and 2018	93
Notes to Consolidated Financial Statements	94

(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	Second Amended and Restated Bylaws of the Registrant, as amended (filed as Exhibit 3.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 5, 2020 (File No. 001-36407) for the quarterly period ended September 30, 2020 and incorporated herein by reference)
4.1	Specimen certificate evidencing shares of common stock (filed as Exhibit 4.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
4.2	Description of Capital Stock (filed as Exhibit 4.2 to the Registrant's Annual Report on Form 10-K filed on February 13, 2020 (File No. 001-36407) for the year ended December 31, 2019 and incorporated herein by reference)
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)

Exhibit No.	Exhibit
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)
10.7**	Amendment to Amended and Restated 2004 Employee Stock Purchase Plan, as amended (filed as Exhibit 10.6 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2020 (File No. 001-36407) for the quarterly period ended June 30, 2020 and incorporated herein by reference)
10.8**	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)
10.9**	Second Amendment to 2018 Stock Incentive Plan, as amended (filed as Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2020 (File No. 001-36407) for the quarterly period ended June 30, 2020 and incorporated herein by reference)
10.10**	Forms of Incentive Stock Option Agreement, Nonstatutory Stock Option Agreements, Restricted Stock Agreement and Restricted Stock Unit Award Agreement under 2018 Stock Incentive Plan, 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)
10.11**	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)
10.12**#	Amended and Restated Annual Incentive Program, as amended
10.13**	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)
10.14**	Letter Agreement between the Registrant and Barry E. Greene dated August 26, 2020 (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on November 5, 2020 (File No. 001-36407) for the quarterly period ended September 30, 2020 and incorporated herein by reference)
10.15**	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)
10.16**	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)
10.17**	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)
10.18**	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)
10.19**	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)
10.20**#	Change in Control Agreement dated November 2, 2020 by and between the Registrant and John M. Maraganore
10.21	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)
10.22	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)

Exhibit No.	Exhibit
10.23	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)
10.24	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)
10.25	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)
10.26	Fifth Amendment to Lease, dated March 27, 2014, by and between the Registrant and ARE-MA Region No. 28, LLC (filed as Exhibit 10.5 to the Registrant's Amendment No. 1 to its Quarterly Report on Form 10-Q/A filed on January 9, 2015 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)
10.27	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)
10.28†	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)
10.29	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)
10.30	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)
10.31	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)
10.32	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)
10.33	First Amendment to Lease entered into between the Registrant and RREEF America REIT II CORP. PPP dated September 30, 2020. (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on November 5, 2020 (File No. 001-36407) for the quarterly period ended September 30, 2020 and incorporated herein by reference)
10.34	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)
10.35	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)
10.36†	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)

Exhibit No.	Exhibit
10.37†	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)
10.38†	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)
10.39	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)
10.40	Exclusive License Agreement for Tuschl II United States Patents and Patent Applications dated as of March 14, 2011, by and between the Registrant and University of Massachusetts (filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on October 2, 2015 (File No. 001-36407) and incorporated herein by reference)
10.41	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)
10.42†	Sublicense Agreement dated effective January 8, 2007 among the Registrant and INEX Pharmaceuticals Corporation (now Arbutus Biopharma Corporation, as successor in interest) (filed as Exhibit 10.38 to the Registrant's Annual Report on Form 10-K filed on February 18, 2011 (File No. 000-50743) for the year ended December 31, 2010 and incorporated herein by reference)
10.43†	Sponsored Research Agreement dated as of July 27, 2009 by and among the Registrant, The University of British Columbia and Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.) (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on June 29, 2011 (File No. 000-50743) and incorporated herein by reference)
10.44†	Supplemental Agreement effective July 27, 2009 by and among the Registrant, Arbutus Biopharma Corporation (formerly Tekmira Pharmaceuticals Corporation), Protiva Biotherapeutics Inc., The University of British Columbia and Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.) (filed as Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed on June 29, 2011 (File No. 000-50743) and incorporated herein by reference)
10.45†	Amendment No. 1, dated as of July 27, 2011, to the Sponsored Research Agreement dated as of July 27, 2009 by and among the Registrant, The University of British Columbia and Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.) (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 3, 2011 (File No. 000-50743) for the quarterly period ended September 30, 2011 and incorporated herein by reference)
10.46†	Cross-License Agreement dated as of November 12, 2012 by and among the Registrant, Arbutus Biopharma Corporation (formerly Tekmira Pharmaceuticals Corporation) and Protiva Biotherapeutics Inc. (filed as Exhibit 10.50 to the Registrant's Annual Report on Form 10-K filed on February 19, 2013 (File No. 000-50743) for the year ended December 31, 2012 and incorporated herein by reference)
10.47†	Settlement Agreement and General Release entered into as of November 12, 2012 by and among Arbutus Biopharma Corporation (formerly Tekmira Pharmaceuticals Corporation), Protiva Biotherapeutics Inc., the Registrant and Acuitas Therapeutics Inc. (formerly AlCana Technologies, Inc.) (filed as Exhibit 10.51 to the Registrant's Annual Report on Form 10-K filed on February 19, 2013 (File No. 000-50743) for the year ended December 31, 2012 and incorporated herein by reference)
10.48	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)
10.49†	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)

Exhibit No.	Exhibit
10.50†	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)
10.51†	License and Collaboration Agreement dated as of February 3, 2013 by and among The Medicines Company and the Registrant (filed as Exhibit 10.2 to the Registrant's Amendment No. 1 to its Quarterly Report on Form 10-Q/A filed on July 26, 2013 (File No. 000-50743) for the quarterly period ended March 31, 2013 and incorporated herein by reference)
10.52	Amendment to License and Collaboration Agreement, dated as of November 22, 2019 between the Registrant and The Medicines Company (filed as Exhibit 10.50 to the Registrant's Annual Report on Form 10-K filed on February 13, 2020 (File No. 001-36407) for the year ended December 31, 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) (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 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, 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 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)

Exhibit No.	Exhibit
10.63†	Purchase and Sale Agreement dated April 10, 2020 between BX Bodyguard Royalties L.P. and the Registrant (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2020 (File No. 001-36407) for the quarterly period ended June 30, 2020 and incorporated herein by reference)
10.64*	Credit Agreement dated April 10, 2020 by and among the Registrant, as Borrower, the Guarantors from time to time party thereto, the Lenders from time to time party thereto, and Wilmington Trust, National Association, as Administrative Agent (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2020 (File No. 001-36407) for the quarterly period ended June 30, 2020 and incorporated herein by reference)
10.65*	First Amendment to Credit Agreement by and among the Registrant, as Borrower, the Guarantors from time to time party thereto, the Lenders from time to time party thereto, and Wilmington Trust, National Association, as Administrative Agent dated August 15, 2020 (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on November 5, 2020 (File No. 001-36407) for the quarterly period ended September 30, 2020 and incorporated herein by reference)
10.66	Stock Purchase Agreement by and among the Registrant, as Borrower, and the investors listed in Exhibit A thereto, dated April 10, 2020 (filed as Exhibit 4.2 to the Registrant's Registration Statement on Form S-3 filed on June 5, 2020 (File No. 333-238989) and incorporated herein by reference).
10.67*†	Co-Development Agreement between the Registrant and BXLS V Bodyguard – PCP L.P. and BXLS Family Investment Partnership V – ESC L.P. dated August 15, 2020 (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 5, 2020 (File No. 001-36407) for the quarterly period ended September 30, 2020 and incorporated herein by reference)
10.68†	Patent Cross-License Agreement dated April 3, 2020 between Dicerna Pharmaceuticals, Inc. and the Registrant (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2020 (File No. 001-36407) for the quarterly period ended June 30, 2020 and incorporated herein by reference)
21.1#	Subsidiaries of the Registrant
23.1#	Consent of PricewaterhouseCoopers LLP, an Independent Registered Public Accounting Firm
31.1#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)- 14(a)/15d-14(a), by Principal Executive Officer
31.2#	Certification pursuant to Section 302 of the Sarbanes-Oxley Act of 2002, Rule 13(a)- 14(a)/15d-14(a), by Principal Financial Officer
32.1#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Executive Officer
32.2#	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Financial Officer
101.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 because such information (i) is not material and (ii) would likely cause competitive harm to the Registrant if publicly disclosed.
#	Filed herewith.

ITEM 16. FORM 10-K SUMMARY

Not applicable.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized, on February 11, 2021.

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 11, 2021.

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/ Olivier Brandicourt, M.D. Olivier Brandicourt, M.D.	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/ Amy W. Schulman Amy W. Schulman	Director
/s/ Phillip A. Sharp, Ph.D. Phillip A. Sharp, Ph.D.	Director

MANAGEMENT TEAM

John M. Maraganore, PhD
Chief Executive Officer
& Director

Yvonne L. Greenstreet, MBChB, MBA
President & Chief
Operating Officer

Akshay K. Vaishnaw, MD, PhD
President, Research
& Development

Pushkal Garg, MD
Chief Medical Officer

Laurie B. Keating, JD
Chief Legal Officer
& Secretary

Al Boyle, PhD
Chief Technical Operations
& Quality Officer

Jeffrey V. Poulton, MBA
Chief Financial Officer

Kelley Boucher
Chief Human Resource
Officer

Tolga Tanguler, MBA
Chief Commercial
Officer

BOARD OF DIRECTORS

Michael W. Bonney, Chair
Board Chair, and former Executive Chair and Chief Executive Officer of Kaleido Biosciences; Board Chair of Magenta Therapeutics; Director of Bristol Myers Squibb Company; former Chief Executive Officer and Director of Cubist Pharmaceuticals; former Director of Sarepta Therapeutics and Syros Pharmaceuticals.

Dennis A. Ausiello, MD
Director of the Center for Assessment Technology and Continuous Health (CATCH); Jackson Distinguished Professor of Clinical Medicine at Harvard Medical School; Physician-in-Chief Emeritus at Massachusetts General Hospital; Member of the Institute of Medicine of the National Academy of Sciences and the American Academy of Arts and Sciences; Director of Seres Therapeutics.

Olivier Brandicourt, MD
Senior Advisor at Blackstone Group; former Chief Executive Officer and Director of Sanofi; former Chief Executive Officer and Chair of Bayer HealthCare; former President and General Manager of the Emerging Markets and Established Products business units; member of the Executive Leadership Team of Pfizer Inc.

Marsha H. Fanucci
Former Chief Financial Officer of Millennium Pharmaceuticals; Chair of the Board of Directors of Cyclerion Therapeutics; Director of Syros Pharmaceuticals and Forma Therapeutics.

Margaret A. Hamburg, MD
Former Commissioner of the U.S. Food & Drug Administration (FDA); Interim Vice President, Global Biological Policy and Programs at the Nuclear Threat Initiative; former Foreign Secretary of the National Academy of Medicine (NAM); former Chair of the Board of the American Association for the Advancement of Science (AAAS).

John M. Maraganore, PhD
Chief Executive Officer of Alnylam; Member of the Board of Directors of Agios Pharmaceuticals; Member and former Chair of the Biotechnology Industry Organization (BIO).

Steven M. Paul, MD
Chairman of the Board, President and Chief Executive Officer of Karuna Therapeutics and board member of Voyager Therapeutics, Inc.; Venture Partner at Third Rock Ventures; co-founder and Director of SAGE Therapeutics; trustee for the Foundation for the National Institute of Mental Health (NIH); former President of the Lilly Research Laboratories of Eli Lilly and Company; former Scientific Director of the National Institute of Mental Health and adjunct professor of Psychiatry at Washington University of St. Louis School of Medicine.

David E.I. Pyott
Former Chair and Chief Executive Officer of Allergan; Member of the Supervisory Board of Royal Philips in the Netherlands; Director of BioMarin Pharmaceutical and Pliant Therapeutics; former Lead Director of Avery Dennison Corporation.

Colleen F. Reitan
Former President of Plan Operations and Chief Operating Officer of Health Care Service Corporation (HCSC); former President and Chief Operating Officer of Blue Cross Blue Shield of Minnesota; Director of Myriad Genetics and Cricket Health.

Amy W. Schulman
Managing Partner, Polaris Partners; Co-founder, Executive Chair, and former Chief Executive Officer of Lyndra Therapeutics; Chair of SQZ Biotech; Senior Lecturer at Harvard Business School; former Executive Vice President and General Counsel of Pfizer; served as the Business Unit Lead for Pfizer Consumer Healthcare.

Phillip A. Sharp, PhD
Institute Professor, The Koch Institute for Integrative Cancer Research, MIT; Founding Director of McGovern Institute for Brain Research, MIT; Nobel Laureate; Founder of Alnylam; Co-founder and former Director of Biogen; Member of the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences; Director of Syros Pharmaceuticals and Vir Biotechnology.

To those who say “impossible, impractical, unrealistic,” we say:

CHALLENGE ACCEPTED

We’re relentless in our pursuit of new treatments because patients shouldn't have to wait for hope.

CONNECT WITH US

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Alnylam® PHARMACEUTICALS

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