2021 Annual Report

CELEBRATING

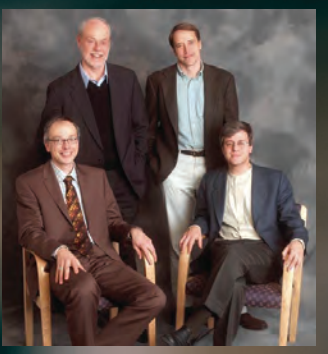
20 YEARS

AND WHAT'S NEXT IN THE

RNAi Revolution

Alnylam®@20

COLIN (U.S.), DIAGNOSED WITH
ACUTE HEPATIC PORPHYRIA



Alnylam's founders: Phillip Sharp, Thomas Tuschl, David Bartel, Phillip Zamore. Not in photo: Paul Schimmel

What started as a hypothesis has become a revolution in the way medicine treats disease.

1999–2001
The future founders of Alnylam perform early experiments using RNAi

2002
Alnylam is founded on June 14th to harness RNAi as a revolution in human health

2003–2004
Ribopharma AG acquisition; first of several partnerships (Merck); Alnylam IPO

2005
First RNAi clinical program (ALN-RSV01)

2006
Zimmerman, et al, paper in *Nature* details proof-of-concept (POC) for RNAi in non-human primates

2012
ALN-TTR02 demonstrates first human POC for RNAi; Alewife manufacturing facility opens

2013–14
First human POC for GalNAc conjugates; Genzyme and The Medicines Company alliances

2016
Groundbreaking on Alnylam's state-of-the-art Norton manufacturing facility; first Alnylam international office

2017
First positive Phase III for Alnylam and RNAi (APOLLO); Vir alliance

2018
ONPATTRO® approved – first-ever approved RNAi therapeutic and Alnylam's first commercial medicine

2019–22
GIVLAARI®, OXLUMO® and Leqvio®* approved – second through fourth-approved RNAi therapeutics; Regeneron alliance; Blackstone collaboration

2022 & Beyond
As we celebrate our 20th anniversary, we look forward with great anticipation for what's next in the RNAi Revolution, including multiple Alnylam development candidates in both rare and larger-population diseases

*Licensed to Novartis

TO OUR STOCKHOLDERS

A Year of Strong Commercial Performance and Significant Pipeline Advancements.

2021 marked a historic chapter in our Company's journey. It was a year in which we saw tremendous progress with our commercial and pipeline performance, along with important steps forward in cementing the next phase of the Company's history with our five-year *Alnylam P^{5}x25* strategy. We believe these, coupled with so many other exciting developments, have poised Alnylam for continued success in 2022, the year that we'll celebrate our 20th anniversary of pioneering an *RNAi Revolution*.

Thus, it is my privilege to write to you as the new CEO of Alnylam, having taken the helm from Dr. John Maraganore, who led this company from its founding in 2002.

Let me begin by reflecting on the commercial successes of our wholly owned marketed medicines, where we achieved $662 million in global net product revenue. This represents 83% year-over-year growth, with a total of over 2,540 patients now receiving our approved RNAi therapies across the three brands: ONPATTRO® (patisiran), GIVLAARI® (givosiran) and OXLUMO® (lumasiran). These results underscore strong patient demand for our products, continuous progress in patient diagnosis, and innovation in market access.

Of course, a key milestone of the year was the historic regulatory approval granted to our partner, Novartis, by the U.S. Food and Drug Administration (FDA) for Leqvio® (inclisiran), the fourth Alnylam-discovered RNAi therapeutic approved in the United States, and the first and only to lower low-density lipoprotein cholesterol (LDL-C, also known as "bad cholesterol") for the treatment of adults with clinical atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia who require additional lowering of LDL-C. We believe the approval of Leqvio affirms the future potential of RNAi therapeutics in large population diseases and facilitates Alnylam's advancement toward its bold *Alnylam P^{5}x25* strategy and goals.

4

APPROVED PRODUCTS IN THE U.S., EU, AND OTHER COUNTRIES, ALL IN THE PAST 4 YEARS

20

2022 MARKS OUR 20TH YEAR AS A COMPANY

"I can say with pride and complete confidence that Alnylam will continue to lead the RNAi revolution with the same tenacity and spirit of innovation that served us so well in our first 20 years."

DR. YVONNE GREENSTREET, CEO

"Alnylam's vision of harnessing the power of RNAi for human health will continue to open up new frontiers of possibility."

Turning to our pipeline, we made great strides across our transthyretin amyloidosis franchise. We are continuing to evaluate the safety and efficacy of patisiran in the APOLLO-B Phase 3 study in transthyretin-mediated (ATTR) amyloidosis patients with cardiomyopathy with the hope of extending the benefit of ONPATTRO to patients with cardiovascular manifestations of ATTR amyloidosis. We completed enrollment in APOLLO-B in the summer of 2021, with results anticipated in mid-2022. Similarly, in August 2021, we completed enrollment in the HELIOS-B Phase 3 study of vutrisiran, our quarterly, subcutaneously administered RNAi therapeutic in development for the treatment of patients with ATTR amyloidosis with cardiomyopathy. If positive, the HELIOS-B study would support our efforts to advance the development of an industry-leading franchise of RNAi therapeutics for the treatment of ATTR amyloidosis. We are one step closer to this goal with the positive results that we recently reported from the HELIOS-A Phase 3 study of vutrisiran, demonstrating reductions in neurologic impairment, with evidence of reversal of polyneuropathy manifestations of disease, improvements in quality of life, and favorable effects on exploratory cardiac endpoints.

There was also great forward momentum for lumasiran throughout 2021. Given the spectrum of disease severity in patients with primary hyperoxaluria type 1 (PH1), we committed to evaluating the efficacy of lumasiran in patients of all ages with advanced PH1, including patients on dialysis. In 2021, having reported on positive results from the ILLUMINATE-C Phase 3 study and based on these data, we submitted supplemental regulatory filings to the U.S. and EU regulatory authorities to support label expansions for OXLUMO. Concurrently, we set out to pursue a compelling life-cycle opportunity for lumasiran in patients with recurrent kidney stone disease and recently initiated a Phase 2 POC study to evaluate this opportunity in non-PH1 patients with chronic kidney stones—an exciting program that we believe could position lumasiran for entry into the prevalent disease market.

5

NEW CLINICAL PROGRAMS ADDED IN 2021

$2.4

BILLION IN CASH, CASH EQUIVALENTS AND MARKETABLE SECURITIES AT YEAR-END 2021

With regard to our earlier stage programs, we are particularly excited by our progress with zilebesiran, our investigational RNAi therapeutic in development for the treatment of hypertension. We initiated our KARDIA Phase 2 program and reported on positive interim results from the Phase 1 study with the potential for quarterly and potentially biannual dosing. We are also pleased to have submitted our clinical trial authorization filing for our ALN-APP program and initiated a Phase 1 study in patients with early-onset Alzheimer's disease, marking our entry into diseases impacting the central nervous system and opening doors for potential new opportunities pursuing targets in extrahepatic tissues. Similarly, we initiated a Phase 1/2 study for ALN-XDH, our investigational RNAi therapeutic for the treatment of gout, yet another opportunity to evaluate the benefit of RNAi therapeutics in the setting of common diseases. We also shared exciting platform enhancements, including preclinical data with our IKARIA platform and ALN-TTRsc04 therapeutic, demonstrating potential to achieve over 90% target knockdown with an annual dosing regimen. We believe our focus on scientific innovation and our commitment to our vision of harnessing the power of RNAi for human health will continue to open up new frontiers of possibility and will fuel the discovery of new therapeutics for patients around the world for decades to come.

On the business front, we entered into a strategic collaboration with PeptiDream, Inc., to discover and develop peptide-siRNA conjugates for targeted delivery of investigational RNAi therapeutics to tissues outside the liver. In addition, we ended the year with a strong cash position which we believe will bridge us to financial self-sustainability and enable us to realize our *Alnylam P^{5}x25* vision.

Of course, one element that is critical to our ability to

"We are committed to being an ethical, responsible and forward-thinking organization whose priorities extend to our patients, our employees, our science, our communities and our planet."

reach the goals we have set for ourselves is our people. Our employees' passion and dedication to developing transformative medicines for patients is nurtured by our unique culture, which enables us to attract and retain highly talented people and motivates them to bring their best to their work. There were also a number of important announcements related to our management team. Dr. Akshay Vaishnaw was promoted to President, we welcomed Indrani Franchini as our new Chief Legal Officer and Corporate Secretary, and while we bid farewell to Dr. John Maraganore as CEO, he will continue to contribute to Alnylam's success as a member of our Scientific Advisory Board.

In 2021, we continued to grow our investment in Corporate Responsibility (CR) and published our second annual CR Report, highlighting the metrics and measures which were aligned with our commitment to being an ethical, responsible, and forward-thinking organization whose priorities extend to our patients, our employees, our science, our communities and our planet. We also continued to expand on our Diversity, Equity and Inclusion initiatives, and received multiple recognitions, among them inclusion in the Bloomberg Gender Equality Index, inclusion in Seramount 100 Best Companies (formerly Working Mothers) and being voted Best Places to Work for Dads. To add to this list of accolades, we were voted the #1 Largest Employer in *The Boston Globe* Top Places to Work list —our seventh consecutive year making the list—and recognized as a Top Employer by *Science* magazine for the third year in a row.

In closing, I am humbled by everything Alnylam has accomplished and invigorated by the opportunities ahead of us. I am deeply thankful to the people who work at this Company, who continue to drive innovation in the name of patients despite unprecedented challenges, and who continue to lead an *RNAi Revolution*. And thank you to our stockholders for believing in the transformative change that this revolution has the potential to bring to human health.

DR. YVONNE GREENSTREET, CEO

ALNYLAM BY THE NUMBERS

12

programs in clinic
(+5 from 2020)

$662

million in combined product revenues
(83% growth YoY)

30+

countries with commercial presence*
(+4 from 2020)

23

countries with Alnylam offices
(+2 from 2020)

1,850+

employees worldwide
(+600 from 2020)

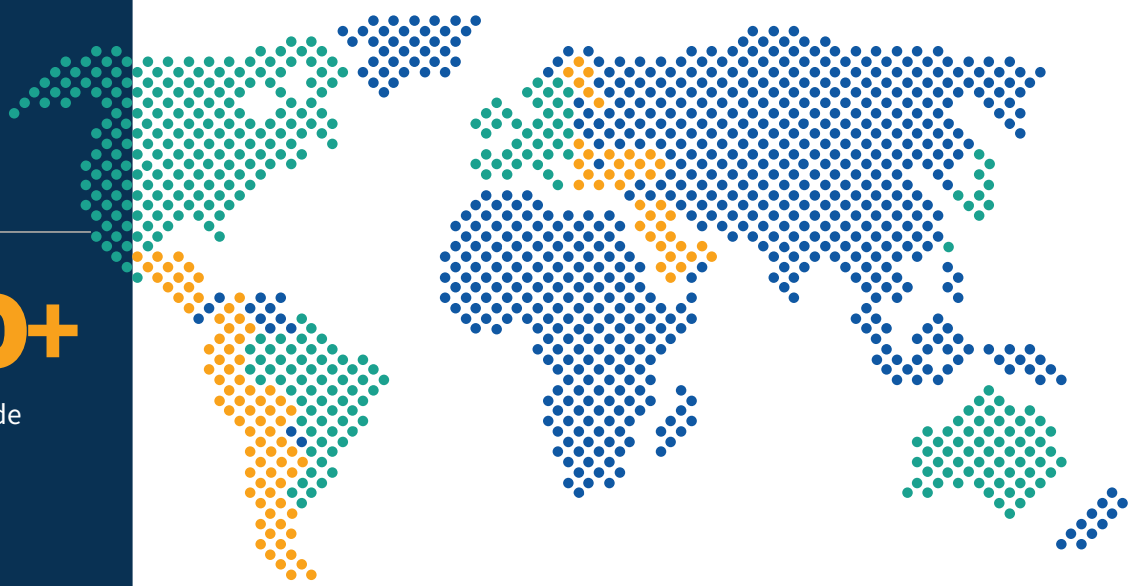
*through direct or distributor relationships

"Our growth is being fueled by our robust pipeline of innovative medicines in both rare and more common diseases and our commitment to sustained innovation across our business."

AKSHAY VAISHNAW, MD, PHD
PRESIDENT, ALNYLAM

ALNYLAM ACROSS THE GLOBE

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



ALNYLAM OFFICES ALNYLAM DISTRIBUTORS

"We've never had this diagnosis before in our family, so it's new to them as much as it is to me. They want to learn as much as they can, so they can support me, even if I don't say that I need them."

SAINT (UK),
DIAGNOSED WITH hATTR AMYLOIDOSIS

Transthyretin-mediated amyloidosis

Transthyretin-mediated (ATTR) amyloidosis is a rare, rapidly progressive, debilitating and fatal disease caused by misfolded transthyretin (TTR) proteins that accumulate as amyloid fibrils in multiple tissues including the nerves, heart, and gastrointestinal tract. There are two types of ATTR amyloidosis: hereditary (hATTR) amyloidosis and wild-type (wtATTR) amyloidosis. Alnylam is building an industry-leading franchise of medicines for the treatment of ATTR amyloidosis, which began with the approval of ONPATTRO® (patrisiran) as a treatment for patients with hATTR amyloidosis with polyneuropathy. The Company is committed to serving all patients with ATTR amyloidosis as it awaits potential regulatory approvals for vutrisiran and continues clinical trials for the treatment of ATTR amyloidosis with cardiomyopathy.

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

ONPATTRO® (patisiran) is an RNAi therapeutic that is approved in the United States and Canada for the treatment of the polyneuropathy of hATTR amyloidosis in adults. ONPATTRO is also approved in the European Union, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with Stage 1 or Stage 2 polyneuropathy, and in Japan for the treatment of hATTR amyloidosis with polyneuropathy.

Vutrisiran is an investigational, subcutaneously administered RNAi therapeutic in development for the treatment of ATTR amyloidosis, which encompasses both hATTR and wtATTR amyloidosis. It is designed to target and silence specific messenger RNA, potentially blocking the production of wild-type and variant TTR protein before it is made. Quarterly and potentially biannual 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.

Vutrisiran is under review by the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Brazilian Health Regulatory Agency and the Japanese Pharmaceuticals and Medical Devices Agency. In the United States, vutrisiran has received an action date under the Prescription Drug User Fee Act of April 14, 2022. The Company received Orphan Drug Designation in Japan for transthyretin type familial amyloidosis with polyneuropathy.

2021 MILESTONES

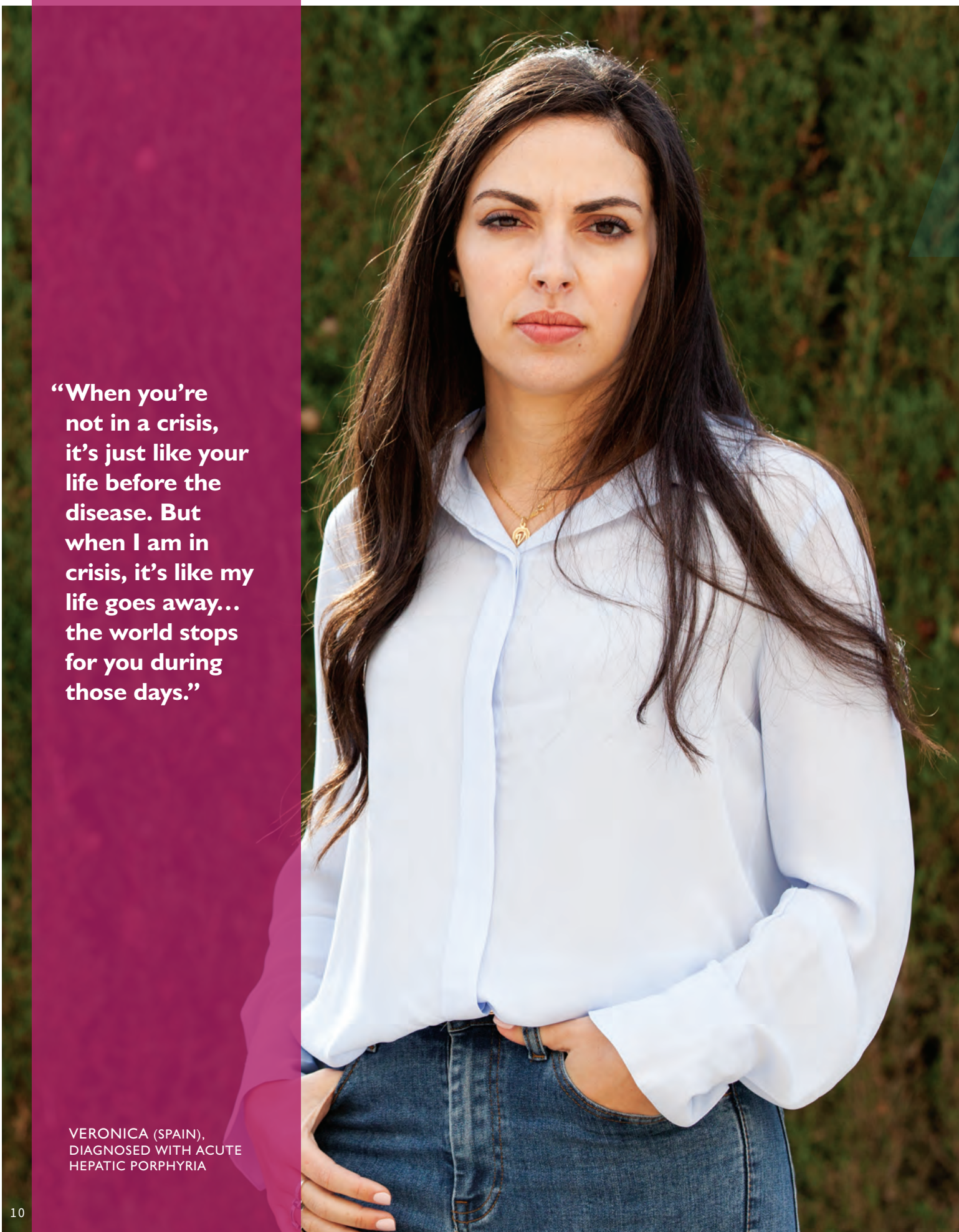
- **Patisiran is currently being evaluated for efficacy and safety in patients with ATTR amyloidosis with cardiomyopathy in the Phase 3 APOLLO-B study.**
- **Filed for regulatory approval for neuropathy in Taiwan.**
- **Positive results from the HELIOS-A Phase 3 study of vutrisiran in patients with hATTR amyloidosis with polyneuropathy at 9 and 18 months were announced.**
- **HELIOS-B, a Phase 3 placebo-controlled mortality and cardiovascular events trial in patients with ATTR amyloidosis with cardiomyopathy, completed enrollment of patients.**

ONPATTRO FACTS

>2,050
patients worldwide on commercial ONPATTRO treatment

>90%
global adherence on commercial ONPATTRO

>30
countries outside the U.S. where ONPATTRO has achieved market access



"When you're not in a crisis, it's just like your life before the disease. But when I am in crisis, it's like my life goes away… the world stops for you during those days."

VERONICA (SPAIN),
DIAGNOSED WITH ACUTE
HEPATIC PORPHYRIA

AHP

Acute hepatic porphyria

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.

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

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

2021 MILESTONES

- **Reported 36-month results from the ENVISION Phase 3 study, demonstrating sustained efficacy and safety with long-term dosing of GIVLAARI.**
- **Received regulatory approvals in Switzerland and Japan.**

300+
patients worldwide on commercial GIVLAARI

10+
Value-based agreements (VBAs) finalized

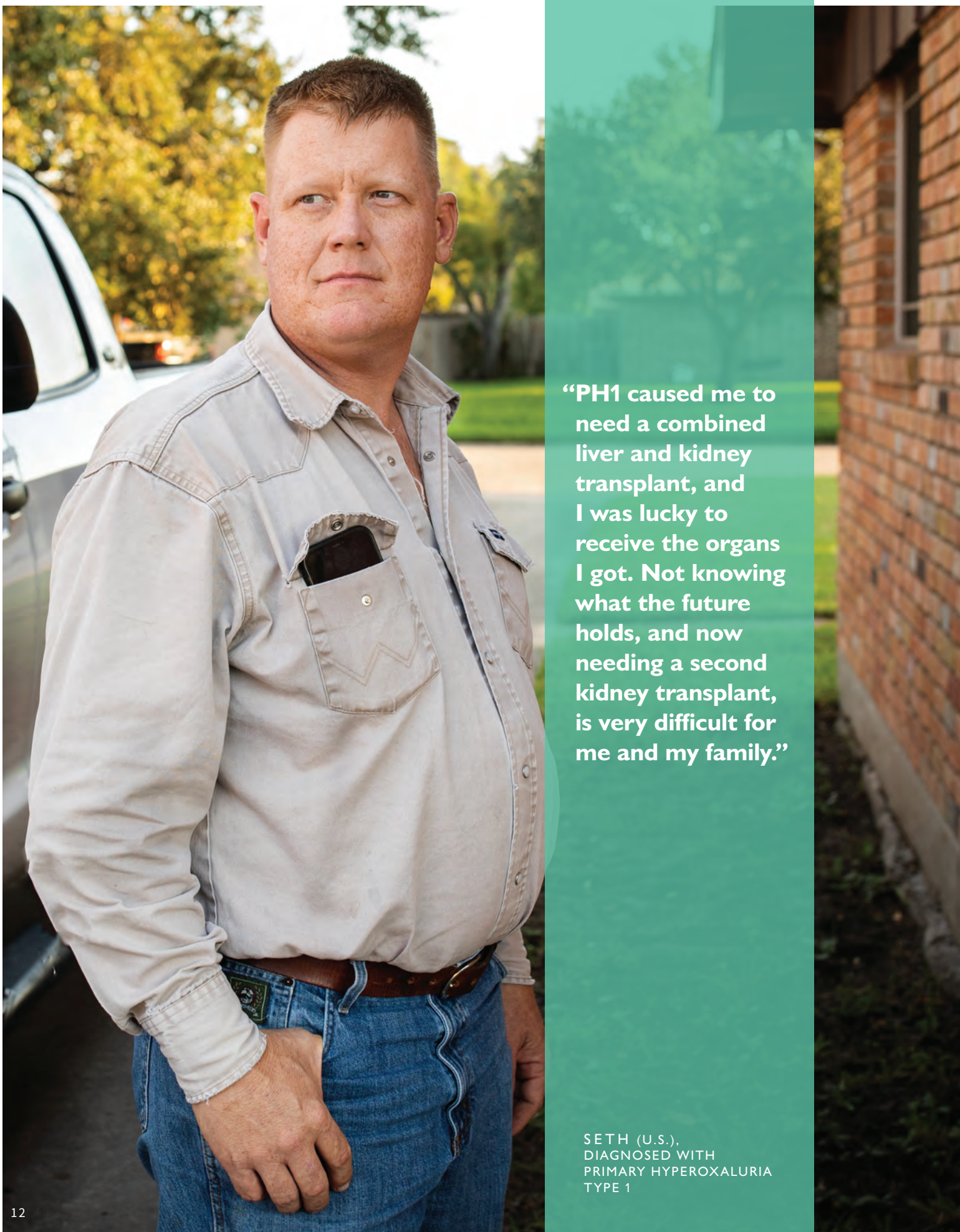
98%
of U.S. lives with confirmed access to GIVLAARI, if prescribed

AHP FACTS

~1k
In the United States and European Union, ~1K people suffer frequent and severe AHP attacks and ~5K people experience one or more AHP attacks annually

15 years
Patients with AHP can wait up to 15 years for a confirmed diagnosis

90%
Severe, unexplained abdominal pain occurs in more than 90% of people who experience AHP attacks



"PH1 caused me to need a combined liver and kidney transplant, and I was lucky to receive the organs I got. Not knowing what the future holds, and now needing a second kidney transplant, is very difficult for me and my family."

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

PH1

Primary hyperoxaluria type 1

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 kidney disease with subsequent accumulation of oxalate throughout the body, including the eyes, bones, skin and the heart, resulting in severe manifestations such as vision loss, bone fractures, skin ulcers and heart failure. PH1 patients in renal failure require a dual liver/kidney transplant.

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

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 United States for the treatment of PH1 to lower urinary oxalate levels in pediatric and adult patients, and in the European Union 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.

2021 MILESTONES

- **Received regulatory approval in Brazil and Switzerland.**
- **Published results from the ILLUMINATE-A Phase 3 study in *The New England Journal of Medicine.***
- **Published results from the ILLUMINATE-B Phase 3 study in *Genetics in Medicine.***
- **Published results from the Phase 1/2 study in the *Clinical Journal of the American Society of Nephrology.***

>140
patients on OXLUMO worldwide

11
VBAs executed as of year-end

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

PH1 FACTS

onset

Majority of patients are diagnosed throughout childhood and adolescence, but patients can present with symptoms at any age, from infancy to late adulthood

symptom

Kidney stones are the most common and early symptom. Recurrent kidney stones are a major cause of morbidity in PH1

regimen

Patients with advanced disease can face an aggressive dialysis regimen of six to seven sessions per week

Other Programs

Zilebesiran is an investigational, subcutaneously administered RNAi therapeutic targeting liver-expressed angiotensinogen in development for the treatment of hypertension.

Hypertension, or high blood pressure, is the leading cause of cardiovascular disease worldwide and a major risk for premature mortality.

Early effects of hypertension can include subtle target organ damage such as left ventricular hypertrophy and cognitive dysfunction. Over time, uncontrolled hypertension can lead to heart failure, atrial fibrillation, valvular heart disease, peripheral arterial disease and aortic syndromes, chronic kidney disease and end-stage renal disease, dementia and Alzheimer's disease. Despite well-established management strategies such as lifestyle modifications and several classes of available antihypertensive treatments, fewer than 20% of people with hypertension have it under control.

2021 MILESTONES

- Initiated KARDIA-1 Phase 2 study evaluating the efficacy and safety of zilebesiran as monotherapy across different doses administered quarterly and biannually.
- Initiated KARDIA-2 Phase 2 study to evaluate the efficacy and safety of zilebesiran administered biannually as a concomitant therapy in patients whose blood pressure is not adequately controlled by standard-of-care antihypertensive medications.
- Reported positive interim Phase 1 data supporting continued development of zilebesiran.

Lumasiran is an investigational, subcutaneously administered RNAi therapeutic targeting hydroxyacid oxidase 1 (HAO1) in development for the treatment of advanced PH1 and recurrent kidney stone disease.

The safety and efficacy of lumasiran in patients with advanced PH1, including patients on dialysis, are currently under review by the FDA and EMA. The safety and efficacy of lumasiran in patients with recurrent kidney stone disease are being evaluated in an ongoing Phase 2 study.

- Reported positive results from the ILLUMINATE-C Phase 3 study in patients of all ages with advanced PH1.
- Submitted a supplemental NDA with the FDA and a Type 2 Variation Filing with the EMA to support label expansion for OXLUMO®.
- Initiated Phase 2 POC study in patients with recurrent kidney stone disease.

EMPLOYEES AT OUR NORTON, MA, (U.S.) MANUFACTURING FACILITY, WHERE DRUG SUBSTANCE FOR MANY ALNYLAM CLINICAL TRIALS IS MADE

Leqvio® (inclisiran) is a subcutaneously administered RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) to reduce low-density lipoprotein cholesterol (LDL-C) levels via an RNAi mechanism of action. Leqvio is developed and commercialized by our partner, Novartis, and is the first and only RNAi therapeutic approved for the treatment of adults with hypercholesterolemia or mixed dyslipidemia. It is also the first RNAi therapeutic approved for a common disease.

2021 MILESTONES

- Our partner, Novartis, received regulatory approval for Leqvio from the U.S. FDA.
- Leqvio is now approved in more than 45 countries.

Fitusiran is an investigational, subcutaneously administered RNAi therapeutic targeting antithrombin (AT) for the treatment of people with hemophilia A and B, with and without inhibitors. Fitusiran, being developed in collaboration with our partner Sanofi, is designed to lower levels of AT with the goal of promoting sufficient thrombin generation to prevent bleeding.

- Sanofi presented new results from the ATLAS Phase 3 program at the 63rd American Society of Hematology.

Cemdisiran is a subcutaneously administered, investigational RNAi therapeutic targeting the C5 component of the complement pathway in development for the treatment of complement-mediated disease. Cemdisiran is currently being advanced by Alnylam as a monotherapy, in patients with immunoglobulin A nephropathy and is also being evaluated by our partner, Regeneron, in combination with pozelimab (REGN3918), an anti-C5 monoclonal antibody, in a Phase 1 study in normal healthy volunteers and patients with paroxysmal nocturnal hemoglobinuria.

- Initiated dosing in a Phase 1 study of combination therapy with pozelimab, an anti-C5 monoclonal antibody, in collaboration with Regeneron.

ALN-HSD is a subcutaneously administered, investigational RNAi therapeutic targeting HSD17B13 in development with our partner, Regeneron, for the treatment of non-alcoholic steatohepatitis (NASH). NASH is a highly prevalent chronic liver disease characterized by the accumulation of fat within hepatocytes, hepatocyte injury and hepatic inflammation, which can lead to progressive fibrosis, cirrhosis and hepatocellular carcinoma.

- Advanced ALN-HSD into Part B of the ongoing Phase 1 study in patients with NASH.

ALN-APP is an investigational, intrathecally administered RNAi therapeutic targeting amyloid precursor protein (APP) in development with Regeneron for the treatment of Alzheimer's disease and cerebral amyloid angiopathy.

- Submitted our Clinical Trial Application (CTA) with plans to initiate a Phase 1 study of ALN-APP, and to initiate the Phase 1 study in patients with early-onset Alzheimer's disease in early 2022.

ALN-XDH is an investigational, subcutaneously administered RNAi therapeutic targeting xanthine dehydrogenase (XDH) in development for the treatment of gout.

- Submitted our CTA to initiate a Phase 1/2 study of ALN-XDH in healthy volunteers and in patients with gout in early 2022.

Our Pipeline

Alnylam's robust clinical development pipeline features multiple late and early stage programs targeting both rare and more prevalent diseases.

FOCUSED IN 4 STRATEGIC THERAPEUTIC AREAS (STArs)

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

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	EARLY/MID STAGE (IND or CTA Filed-Phase 2)	LATE STAGE (Phase 2-Phase 3)	REGISTRATION/ COMMERCIAL[2] (OLE/Phase 4/ITS/registries)	COMMERCIAL RIGHTS
ONPATTRO® (patisiran)[3]	*hATTR Amyloidosis-PN*	✓	✓			●	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]
Vutrisiran	*hATTR Amyloidosis-PN*	✓				●	Global
Patisiran	*ATTR Amyloidosis Label Expansion*	✓			●		Global
Vutrisiran	*ATTR Amyloidosis*	✓			●		Global
Vutrisiran[8]	*Stargardt Disease*	✓			○		Global
Fitusiran	*Hemophilia*	✓			●		15-30% Royalties
Lumasiran	*Severe PH1 Recurrent Renal Stones*	✓		●	●		Global
Cemdisiran (+/- Pozelimab)[9]	*Complement-Mediated Diseases*	✓			●		50/50; Milestone Royalty
Belcesiran[10]	*Alpha-1 Liver Disease*	✓		●			Ex-U.S. option post-Phase 3
ALN-HBV02[11] (VIR-2218)	*Hepatitis B Virus Infection*	✓		●			50-50 option post-Phase 2
Zilebesiran (ALN-AGT)	*Hypertension*	✓		●			Global
ALN-HSD	*NASH*			●			50-50
ALN-APP	*Alzheimer's Disease; Cerebral Amyloid Angiopathy*			●			50-50
ALN-XDH	*Gout*			●			Global

[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 (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 PN

[4] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older

[5] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 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] Phase 3 study of vutrisiran in Stargardt Disease expected to initiate in late 2022

[9] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics

[10] Dicerna is leading and funding development of Belcesiran

[11] Vir is leading and funding development of ALN-HBV02

ALNYLAM SCIENTIST IN OUR LABS IN CAMBRIDGE, MA (U.S.)

STRATEGIC COLLABORATIONS

Work with the best of the best. That's our philosphy when it comes to strategic collaborations. We seek out partners who share our passion for scientific innovation and committment to leveraging talent and resources to make a positive and significant impact on the health of humanity. Our collaborations include R&D, commercial and financing partnerships and population health research consortiums like UK Biobank and Our Future Health.

REGENERON

SANOFI

NOVARTIS

VIR

PeptiDream

(new in 2021)

Blackstone

biobank uk

+ Our Future Health

(new in 2021)

Supporting Patients

From our founding in 2002, our goal has been to help patients live healthier, fuller lives and 20 years later, that remains our focus.

As we grow, both in the number of products we bring to market and geographically, we know that we have the opportunity to increasingly fulfill our founders' vision of bringing the therapeutic potential of RNAi therapeutics to patients worldwide. We're excited about the opportunity to help as many people as possible who previously either had no or limited treatment options for the diseases they're living with.

In order to do so, ensuring access to our medicines for those who may benefit from them has always been our North Star. That's why, before we even had our first approved medicine, we defined a set of access pillars, and committed to publishing our progress against them annually in our Patient Access Philosophy Report.

Learn more about our commitment to patient access and download our 2021 Patient Access Philosophy Report at alnylam.com/access or by scanning this code with your mobile phone.

PATIENT ACCESS BY THE NUMBERS

>43
U.S. VBAs for ONPATTRO®, GIVLAARI® and OXLUMO®

>2,300
patients worldwide receiving commercial Alnylam therapies

30+
markets where patients have direct access or distributor access to Alnylam medicines

>250
U.S. patients enrolled in commercial copy program for ONPATTRO, GIVLAARI and OXLUMO

>88%
of overall U.S. lives* and 65% of European lives with access to Alnylam medicines**

Zero
price increases on three marketed products

*Confirmed access to ONPATTRO, GIVLAARI or OXLUMO across commercial, Medicare, Medicaid, and other government payer categories

** Where Alnylam has a presence and access is granted

PATIENT SERVICES

Alnylam ASSIST®

Alnylam Assist® offers personalized services to patients in the U.S., Canada and Brazil throughout treatment with our medicines. Services include helping patients understand insurance coverage for therapy, informing them of options and eligibility for financial support, providing materials to start conversations with physicians and family members, and sharing information on patient advocacy organizations and other resources.

>920

patients in the U.S. enrolled in Alnylam Assist

Alnylam Act® / GeneAct™

Alnylam Act® offers eligible patients in the U.S., Canada and Brazil no-charge, third-party genetic testing and counseling. In 2021, GeneAct™ was launched. It offers a third-party testing program in Europe and this service is now available in 11 countries. Both programs 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 these programs have no obligation to recommend, purchase, order, prescribe, promote, administer, use, or support any Alnylam product.

>58k

genotyped samples through Alnylam Act and GeneAct programs, resulting in >3,300 positive test results for relevant genetic mutations

GLAUCIENE (BRAZIL), DIAGNOSED WITH AHP

Corporate Responsibility

Since Alnylam's inception, Corporate Responsibility (CR) has been a guiding principle of who we are and how we operate around the globe. Our CR mission statement—"Accepting Challenges to Improve the Health of Humanity"—describes our commitment to tackling unprecedented and complex challenges, taking courageous action, and using our business as a force for good.

Our CR initiatives are organized across five interconnected, stakeholder-related pillars. Each pillar has a guiding imperative, leadership team, and accountability for tracking and managing our impact throughout the year.

"Our desire to make a positive impact on the world extends far beyond what our medicines can do. Every day, as a company, we seek to contribute to the greater good by embracing causes and tackling challenges which will improve our communities and the health of humanity."

ARUN SKARIA | DIRECTOR, CORPORATE SOCIAL RESPONSIBILITY, ALNYLAM

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 2021 CR Report at alnylam.com/responsibility or by scanning this code with your mobile phone.

ALNYLAM CHALLENGERS
A SOCIAL IMPACT INITIATIVE

We launched Alnylam Challengers focused on rallying behind bold, entrepreneurial approaches to increase access to critical health services, medicines, and treatments in underserved communities. Through this program, we empower "Challengers"—social entrepreneurs, employees, business partners and others—in their pursuit of fresh solutions to address health inequities and social determinants of health.

We partnered with, and donated, an initial $1 million to Acumen America, the U.S. division of the pioneering global NGO that invests in social impact-driven companies, leaders and ideas, to impact the health of 75 million people in the U.S. by 2024.

Alnylam Challengers, and our partnership with Acumen represents a multi-dimensional commitment that includes:

- **Social Investment Portfolio**: A strategic social investment model to tackle health inequities by partnering with a diverse and boldly innovative set of social entrepreneurs, enterprises, and non-profit organizations.
- **Advisory Corps**: A skills-based volunteerism initiative where Alnylam employee teams serve as subject-matter expert advisors to address health equity issues through innovative business models.
- **Convenings**: A series of cross-sector forums that embed Alnylam into industry, national, and international dialogue around pressing issues of health equity and rally others to think boldly and partner on important health issues.

Working closely with Acumen America, we seek to raise awareness of systemic health equity issues, advance the work of bold business and nonprofit models, and improve the health of underrepresented people.

ACUMEN
CHANGING THE WAY THE WORLD TACKLES POVERTY

Acumen America's focus in healthcare is to invest in companies that improve outcomes, enhance patient experience and lower costs for low-income Americans.

Watch the Alnylam Challengers video at alnylam.com/responsibility or by scanning this code with your mobile phone.

Our Culture = Our Strength

Despite the challenges presented by the global pandemic over the past two years, our dynamic and inclusive company culture has given us and our employees the strength to support each other and stay true to our mission. In fact, in 2021, the results of our annual employee survey (which was completed by 96% of employees) showed that 90% of employees felt proud to work at Alnylam, 90% felt inspired by their work and 91% felt respected by colleagues. That we've been able to maintain and strengthen our culture during this time period is all the more remarkable given that more than 600 colleagues joined us in the past two years, when approximately three-quarters of our workforce has been working remotely or hybrid.

"Since the start of the pandemic, Alnylam's first priority has been the health and safety of our employees, contractors and their families. As the pandemic evolves, we are providing resources, actively listening, and supporting flexibility for employees to manage all parts of their lives."

KELLEY BOUCHER
CHIEF HUMAN RESOURCES OFFICER, ALNYLAM

SUPPORTING EMPLOYEE WELLBEING

Our employees are committed to our mission, and we're committed to taking care of them and their needs. Throughout the pandemic, we've continually assessed our COVID-19 response plan, our comprehensive benefits and our ways of working and made adjustments and enhancements to maximize retention and ensure that our employees can be as focused as possible on their work.

THANK YOU TO OUR ON-SITE EMPLOYEES

Throughout the pandemic, more than 300 employees, primarily at our R&D and manufacturing sites in the U.S., have been on-site full time (or close to full time). Their commitment to ongoing research and the manufacture of our medicines is emblematic of our devotion to putting patients first.

WORKPLACE RECOGNITION

The Boston Globe
TOP PLACES TO WORK
2015–2021
(7x in a row, including #1 largest employer for 2021)

Science 2021 TOP EMPLOYER
(3x in a row)

Great Place To Work.
(in 9 countries)

Bloomberg Gender-Equality Index 2021
(2x in a row)

FASTCOMPANY
BEST WORKPLACES FOR INNOVATORS 2021

SEAMOUNT 100 BEST COMPANY 2021
(formerly Working Mother Best Workplaces)

SEAMOUNT BEST COMPANY FOR DADS 2021

Best Workplaces™ For Women Medium Organisations
Great Place To Work. UK 2021

Diversity, Equity & Inclusion

We believe that our long-term success and ability to deliver on the promise and potential of RNAi therapeutics requires a diverse, equitable and inclusive workforce. We are committed to building an environment where employees are enabled to achieve their full potential. By empowering employees to bring their unique differences to work, our business grows stronger with advanced and original thinking, allowing us to bring innovative, new medicines to patients and meet our *P^{5}x25* goals.

A FORCE FOR CHANGE

We have been an outspoken voice for DE&I efforts within the biopharmaceutical industry, and as companies across industries and around the globe have increasingly focused on diversity, equity and inclusion both for employees and in their business practices, we have continued to play a leadership role.

"Our commitment to diversity, equity and inclusion focuses on each in relation to the other. Diversity means Alnylam reflects the world we live in. Equity ensures we are all treated fairly and with respect no matter our differences. Inclusion ensures we all bring our authentic selves to work every day. Together, these focus areas ensure alignment with Alnylam's core values and fosters a sense of belonging for our employees."

SARASWATHY (SARA) NOCHUR | CHIEF DE&I OFFICER, ALNYLAM

2021 DE&I HIGHLIGHTS

- Appointed Alnylam's first Chief Diversity, Equity & Inclusion Officer
- Expanded employee programming in DE&I training, accountability and allyship
- Expanded Employee Resource Network (ERN) groups and Initiative Driven Interest Groups (IDIGs) to 7
- Brought together a cross-functional team to develop a DE&I Action Plan that will guide our internal and external efforts in 5 key areas for years to come: Employee Education and Development, Talent Acquisition and Management, Workplace Environment and Policy, Employee Engagement, and Patient and Community Engagement
- Set diversity in recruiting goals for 2021 and 2022

EMPLOYEE FEEDBACK

89%

of employees express that Alnylam supports diversity in our workforce
(2021 Employee Survey)

88%

of employees support Alnylam's efforts to foster an inclusive work culture
(2021 Employee Survey)

LEADING BY EXAMPLE

OUR BOARD OF DIRECTORS

5 **of the 11 members are female**

2 **are from underrepresented* populations**

OUR MANAGEMENT TEAM

3 **of the 8 members are female**

4 **are from underrepresented* populations**

EMPLOYEE RESOURCE NETWORKS

iTHRIVE
(Women at Alnylam)

SHADES
(Alnylam's Multicultural Network)

SAGA
(Sexuality and Gender Alliance)

PTA
(Parenting Together at Alnylam)

AN ALNYLAM DE&I VIRTUAL TOWN HALL WAS ATTENDED BY +250 EMPLOYEES FROM AROUND THE GLOBE

*Defined as those who self-reported as Black or African American, Hispanic or Latino, American Indian, Alaska Native or Pacific Islander, or who identified as two or more races

Alnylam 2021 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, 2021

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

OR

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

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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, a 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, 2021, was $19,996,896,335. 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 4, 2022, the registrant had 120,210,498 shares of Common Stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2022 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, 2021, 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, 2021

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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 novel coronavirus, or 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 effectiveness of vaccination and booster vaccination campaigns, 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, our ability to execute business continuity plans to address disruptions caused by the COVID-19 or any future pandemic, and the success and effectiveness of our return to office initiatives;
- our views with respect to the potential for approved and investigational RNAi therapeutics, including ONPATTRO, GIVLAARI, OXLUMO, Leqvio® (inclisiran), vutrisiran, fitusiran and zilebesiran;
- 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;
- our expectations regarding the ongoing and future regulatory review of vutrisiran;
- our expectations regarding potential market size for, and the successful commercialization of, ONPATTRO, GIVLAARI, OXLUMO, Leqvio 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 partners' ability with respect to Leqvio and fitusiran;
- the progress of our research and development programs, including programs in both rare and prevalent diseases;
- the potential for improved product profiles to emerge from our new technologies, including our IKARIA and GEMINI platforms and our ability to successfully advance our delivery efforts in extrahepatic tissues;
- 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, including vutrisiran (or other products 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 OXLUMO and ONPATTRO (and vutrisiran, if approved) 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, including vutrisiran, and, our, or with respect to Leqvio 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^{5}x25* strategy and our intentions to achieve the metrics associated with this strategy, including to become a top five biotech company 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 or of any current or future government investigation, including any investigation related to the subpoena received on or about April 9, 2021 pertaining to our marketing and promotion of ONPATTRO in the United States, or U.S.;
- 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.

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 ribonucleic acid 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 the cause or pathway of 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 based on a hexadecyl (C16) moiety as a lipophilic ligand. During 2021, we also advanced approaches for lung, muscle and adipose tissue delivery of siRNAs. Our focus is on clinical indications where there is a high unmet need, a genetically validated target, 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.

Based on our track record of setting and exceeding five-year goals, in 2021, we launched our *Alnylam P^{5}x25* 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^{5}x25*, we aim to deliver transformative rare and prevalent disease medicines for patients around the world through sustainable innovation, while delivering exceptional financial performance. 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

We ended 2021 making meaningful progress towards these goals, with four marketed products and 13 clinical programs, including five 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 hereditary transthyretin-mediated amyloidosis, or 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 multiple additional countries, including Brazil. Regulatory filings in other territories are pending and additional filings are planned for 2022 and beyond. GIVLAARI is approved in the U.S. for the treatment of adults with acute hepatic porphyria, or AHP, in the EU for the treatment of AHP in adults and adolescents aged 12 years and older, and in several additional countries, including Brazil, Canada, Switzerland and Japan. We have also filed for regulatory approval for givosiran (the non-branded drug name for GIVLAARI) in Colombia and additional regulatory filings are pending or planned for 2022 and beyond. In November 2020, we received regulatory approval for OXLUMO in the U.S. and EU for the treatment of primary hyperoxaluria type 1, or PH1, in all age groups. In June 2021, we received marketing authorization approval for OXLUMO in Brazil for the treatment of PH1 in both children and adult patients. Regulatory filings in other territories are pending and additional filings are planned for 2022 and beyond.

Our fourth product, Leqvio (inclisiran), is being developed and commercialized by our partner Novartis AG, or Novartis, and has 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. In July 2021, Novartis announced that the resubmission to the FDA for the inclisiran NDA to address the complete response letter was filed, and listed its own site in Schaftenau, Austria, as the manufacturing location for the final finished product within its NDA resubmission. In December 2021, Leqvio was approved by the FDA as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia, or HeFH, or clinical atherosclerotic cardiovascular disease, or ASCVD, who require additional lowering of LDL-C. As of January 2022, Leqvio has been approved in more than 50 countries.

In addition to our marketed products, we have five late-stage investigational programs advancing toward potential commercialization. These programs include our wholly owned programs: 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 and Stargardt Disease; as well as fitusiran for the treatment of hemophilia, which is being advanced by our partner Genzyme Corporation, a Sanofi company, or Sanofi, and cemdisiran for the treatment of complement-mediated diseases, which is being advanced by our partner Regeneron Pharmaceuticals, Inc., or Regeneron, in a Phase 3 study of cemdisiran and pozelimab combination in myasthenia gravis.

In further support of our *Alnylam P^{5}x25* strategy and in view of our evolving risk profile, we remain focused on continued evolution of our global infrastructure, including key objectives such as optimizing our global structure for execution in key markets, enhancing performance consistent with our values, and continuing to strengthen our culture. We maintain focus on our global compliance program to drive its evolution and enhancement in view of the *Alnylam P^{5}x25* strategy. Building from our global Code of Business Conduct and Ethics, our compliance program is designed to empower our employees and those with whom we work to execute on our strategy consistent with our values and in compliance with applicable laws. Comprised of components such as risk assessment and monitoring; policies, procedures, and guidance; training and communications; dedicated resources; and systems and processes supporting activities such as third party relationships and investigations and remediation; our program and related controls are built to enhance our business processes, structures, and controls across our global operations.

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, Novartis (which acquired our partner The Medicines Company, or MDCO, in 2020), Sanofi, Vir Biotechnology, Inc., or Vir, Dicerna Pharmaceuticals, Inc. (acquired by Novo Nordisk A/S, or Novo Nordisk, in December 2021), or Dicerna, and PeptiDream, Inc., or PeptiDream.

The COVID-19 Pandemic

In March 2020, the World Health Organization declared the outbreak of COVID-19 as a pandemic. More recently, other, more infectious, variants of COVID-19 have been identified, which continue to spread 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. Since the onset of the global pandemic in 2020, we have been closely monitoring the spread of COVID-19 and its variants, 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 caused us to modify our business practices, including implementing a temporary global work from home policy in March 2020 for all employees who were able to perform their duties remotely and temporarily 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 appropriate safety precautions based on vaccination rates and local guidance, and in October 2021, we formally re-opened our offices in the U.S., following openings in other territories, to those employees who have been fully vaccinated. The effects of the COVID-19 pandemic continue to evolve and, at this time, we cannot predict when certain restrictions that remain in place to protect our employees, customers and patients will no longer be needed. Recognizing that local conditions vary for our offices around the world and that the trajectory of the virus continues to be uncertain, we may adjust our plans for employees returning to our offices as deemed necessary. Since early 2021, global vaccination efforts have been underway to control the pandemic. However, 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 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 effectiveness of vaccination and booster vaccination campaigns, 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 2021 and Recent Highlights

TTR Franchise

- ***ONPATTRO (patisiran) – hATTR Amyloidosis with Polyneuropathy***
  - Recognized ONPATTRO global net revenue of $474.7 million for the year ended December 31, 2021
  - Attained over 2,050 patients worldwide on commercial ONPATTRO treatment as of December 31, 2021
- ***Vutrisiran – ATTR Amyloidosis and Stargardt Disease***
  - Reported positive results for 18-month endpoints and safety from the HELIOS-A Phase 3 study in hATTR amyloidosis patients with polyneuropathy
  - Submitted a JNDA in Japan for the treatment of hATTR amyloidosis patients with polyneuropathy
  - Introduced new near-term opportunity for vutrisiran in Stargardt disease, expected to enter Phase 3 development in late 2022

Commercial/Late-Stage Pipeline

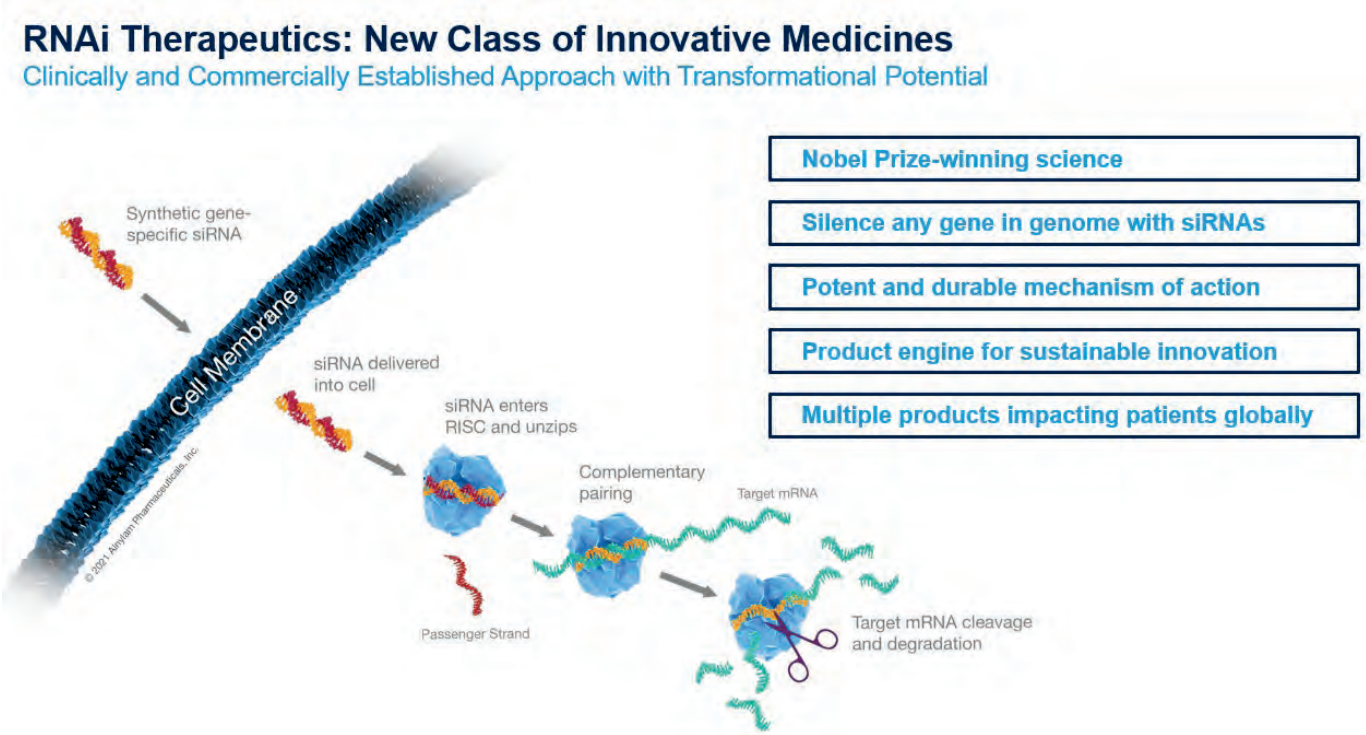
- ***GIVLAARI (givosiran) – Acute Hepatic Porphyria***
  - Recognized GIVLAARI global net revenue of $127.8 million for the year ended December 31, 2021
  - Attained over 350 patients worldwide on commercial GIVLAARI treatment as of December 31, 2021
- ***OXLUMO (lumasiran) – Primary Hyperoxaluria Type 1***
  - Recognized OXLUMO global net revenue of $59.6 million for the year ended December 31, 2021
  - Attained over 140 patients worldwide on commercial OXLUMO treatment as of December 31, 2021
- ***Leqvio (inclisiran) – Hypercholesterolemia (in collaboration with Novartis)***
  - Our partner, Novartis, received FDA approval for Leqvio as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD who require additional lowering of LDL-C
  - We recognized a $25 million milestone payment from Novartis related to the FDA approval of Leqvio in December 2021
- ***Lumasiran – Advanced Primary Hyperoxaluria Type 1 and Recurrent Kidney Stone Disease***
  - Reported positive topline results from the ILLUMINATE-C Phase 3 study in patients with advanced PH1
  - Submitted regulatory applications to the FDA and European Medicines Agency, or EMA, to support label expansion for OXLUMO for the treatment of advanced PH1
  - Initiated a Phase 2 study in patients with recurrent kidney stone disease
- ***Fitusiran - Hemophilia (in collaboration with Sanofi)***
  - Our partner, Sanofi, reported positive results from the Phase 3 ATLAS-A/B and ATLAS-INH studies, demonstrating fitusiran significantly reduced bleeds in people with hemophilia A or B, with or without inhibitors

Early-Stage and Pre-Clinical Pipeline

- ***Cemdisiran*** for the treatment of complement-mediated diseases; our partner, Regeneron, initiated Phase 3 studies of cemdisiran and pozelimab combination in myasthenia gravis and paroxysmal nocturnal hemoglobinuria
- ***Zilebesiran (ALN-AGT)*** for the treatment of hypertension; initiated KARDIA-2 Phase 2 combination therapy study of zilebesiran in patients with inadequately controlled hypertension

Corporate Highlights

- ***Finance***
  - Ended 2021 with $2.44 billion in cash, cash equivalents and marketable securities
- ***Business***
  - Announced the planned transition of founding CEO John Maraganore, Ph.D., to Yvonne Greenstreet, MBChB effective January 1, 2022



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. We believe this success will enable us to achieve our *Alnylam P*^{5}*x25* strategy under which we expect to sustainably and organically create and commercialize transformative rare and prevalent disease medicines benefiting hundreds of thousands of patients around the world while delivering strong financial performance, 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 more 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, zilebesiran (formerly ALN-AGT), ALN-HBV02 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 extrahepatic delivery, including delivery to the brain and spinal cord, as well as ocular delivery. During 2021, we presented data utilizing an alternative conjugate approach based on a hexadecyl (C16) moiety as a lipophilic ligand, with proof-of-concept, or POC, demonstrated in rodent and non-human primates. C16 conjugates provide robust CNS knockdown with wide biodistribution and long duration of action, and this technology enabled 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. We are continuing to advance other extrahepatic delivery approaches, including delivery to muscle and adipose cells, as well as lung delivery. In addition, we are exploring peptide and antibody-based approaches for targeted siRNA delivery to new tissues, and in 2021 we entered into a license and collaboration agreement

with PeptiDream to discover and develop peptide-siRNA conjugates for targeted delivery of RNAi therapeutics to a broader range of extrahepatic tissues.

In 2021, we unveiled our IKARIA™ platform harboring further chemistry advancements that enables robust target knockdown with an annual dosing regimen. We also unveiled an additional technology platform, GEMINI™, that we believe has the potential to simultaneously silence two unique gene transcripts using a single chemical entity. We believe that this platform, could have potential applications in cardiometabolic, CNS, oncologic, and viral diseases.

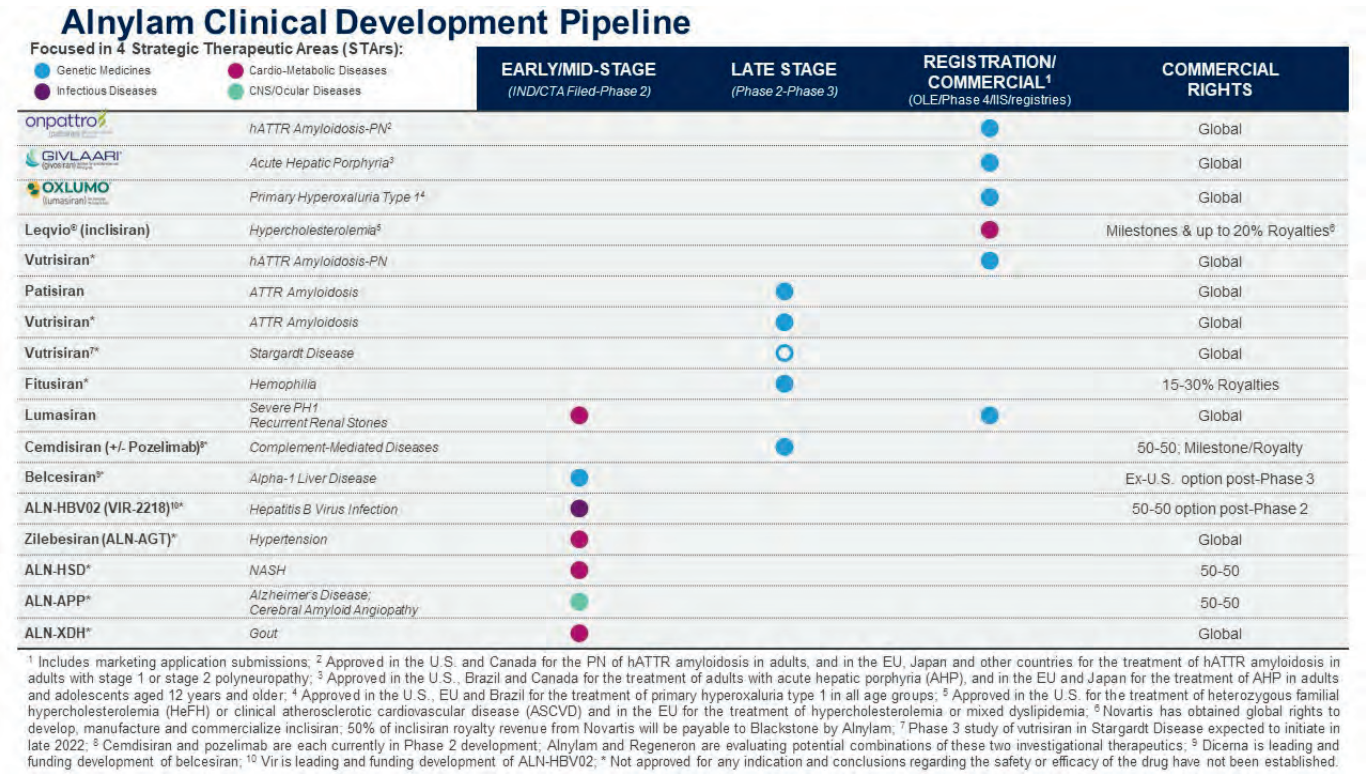
Finally, we continue to leverage human genetics to advance our efforts to bring innovative medicines to patients. We have established a relationship with the UK BioBank to support the sourcing of novel, genetically validated targets and secure access to databases of genetic information. In 2021, we furthered this effort through our partnership with Our Future Health to support the design and delivery of the research program to recruit up to five million adults from across the UK. Coupled with our proven ability to uncover novel gene targets, we believe our approach, investments and commitment to genetically validated targets has the potential to increase our success rate, streamline clinical trials and speed the development of precision medicines for patients with both rare and prevalent diseases.

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, validating our approach to drug development. Moreover, we believe that our reproducible and modular platform will support our *Alnylam P*^{5}*x25 s*trategy under which we expect to sustainably and organically create and commercialize transformative rare and prevalent disease medicines benefiting hundreds of thousands of patients around the world while delivering strong financial performance, 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, 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, 2022. It identifies those programs for which we have received marketing approval, the stage of our programs and our commercial rights to such programs:



[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 and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S., EU and Brazil for the treatment of primary hyperoxaluria type 1 in all age groups; [5] Approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia; [6] 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; [7] Phase 3 study of vutrisiran in Stargardt Disease expected to initiate in late 2022; [8] Cemdisiran and pozelimab are each currently in Phase 2 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics; [9] Dicerna is leading and funding development of belcesiran; [10] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

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 each case in certain territories for the specific indications approved in each such territory, 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 2022.

Patisiran (the non-branded name for ONPATTRO) is also being investigated in a Phase 4 study in patients with polyneuropathy of hATTR amyloidosis due to a T60A or V122I variant.

Patisiran – ATTR Amyloidosis with Cardiomyopathy

Patisiran has received Orphan Drug Designations in the U.S., EU and Japan; specific Orphan Drug Designations vary by country/region.

Patisiran is being investigated in patients with ATTR amyloidosis (wild-type or hereditary) with cardiomyopathy in the ongoing APOLLO-B Phase 3 study.

APOLLO-B Phase 3 Study

In September 2019, we initiated APOLLO-B, a randomized, double-blind, placebo-controlled Phase 3 study designed to evaluate the efficacy and safety of patisiran in patients in ATTR amyloidosis patients with cardiomyopathy. The study enrolled 360 adult patients with confirmed cardiomyopathy and medical history of symptomatic heart failure due to ATTR amyloidosis, with enrollment completed in the second quarter of 2021. Patients were randomized 1:1 to patisiran or placebo. Concomitant use of on-label commercially available tafamidis is not prohibited, but is capped at 30 percent at baseline. 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. Topline results are expected in mid-2022.

Vutrisiran – ATTR Amyloidosis and Stargardt Disease

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, in the liver. Quarterly, and potentially 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 April 2021, we reported positive 9-month results from our HELIOS-A Phase 3 study of vutrisiran in patients with hATTR amyloidosis with polyneuropathy, and based on these positive data, we submitted an NDA with the FDA for the approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults. In June 2021, the FDA accepted our NDA submission for review for vutrisiran, with an action date set for April 14, 2022 under the Prescription Drug User Fee Act, or PDUFA. In September 2021, we submitted a marketing authorisation application, or MAA, to the EMA. Vutrisiran is also under regulatory review by the Brazilian Health Regulatory Agency, or ANVISA and Pharmaceuticals and Medical Devices Agency, or PMDA, in Japan. 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 timed 10-meter walk test, both compared to external placebo. Changes from baseline in NT-proBNP were evaluated as an exploratory endpoint at nine months. Additional secondary and exploratory endpoints were evaluated at 18 months. In addition, following the 18-month treatment period, all patients are eligible to receive vutrisiran for an additional 18 months as part of the randomized treatment extension where they will receive either 25mg vutrisiran once quarterly or 50mg vutrisiran once every six months.

- *Efficacy and Safety Results:*

  In April 2021, we reported positive 9-month results from our HELIOS-A Phase 3 study of vutrisiran in patients with hATTR amyloidosis with polyneuropathy. The 9-month results achieved the study's primary endpoint, with vutrisiran showing improvement in the mean change from baseline in mNIS+7 as compared to external placebo data from the APOLLO Phase 3 study of patisiran. At 9 months, vutrisiran also met all secondary endpoints, demonstrating improvement in quality of life as assessed by the Norfolk QoL-DN instrument and improvement in gait speed as assessed by the timed 10-meter walk test, both compared to the external placebo group. The majority of patients

experienced improvement in neuropathy and in quality of life, both relative to baseline, showing the potential for vutrisiran to reverse polyneuropathy manifestations of hATTR amyloidosis. Vutrisiran also demonstrated an encouraging safety profile with no drug-related discontinuations or deaths. 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 safety signals regarding hematology, renal function or liver function tests. Based on these positive data, in April 2021, we submitted an NDA with the FDA for the approval of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis in adults, with an action date under PDUFA of April 14, 2022. Vutrisiran is also under regulatory review by the EMA, ANVISA and PMDA.

In January 2022, we reported positive 18-month results from the HELIOS-A study. At 18 months, the study met all secondary endpoints measured, including statistically significant improvements in neuropathy as measured by mNIS+7, quality of life, gait speed, nutritional status and overall disability, relative to external placebo data from the APOLLO Phase 3 study of patisiran. Vutrisiran continued to demonstrate halting or reversal of polyneuropathy, with improvements in neuropathy impairment and quality of life relative to baseline. The final secondary endpoint, reduction in serum TTR levels with vutrisiran, demonstrated non-inferiority relative to the within-study patisiran arm, as expected. Vutrisiran achieved a rapid and sustained reduction of serum TTR at 18 months, with a mean reduction from baseline of 88 percent. In addition, patients treated with vutrisiran showed improvements in exploratory endpoints, including the biomarker NT-proBNP and certain echocardiographic parameters, relative to placebo, and an improvement in technetium uptake relative to baseline in a majority of patients in a planned cohort, providing potential evidence for reduced cardiac amyloid burden and for vutrisiran to improve cardiac manifestations of disease. Vutrisiran continued to demonstrate an encouraging safety and tolerability profile. There were three study discontinuations (2.5 percent) due to AEs in the vutrisiran arm during the 18-month treatment period; one due to a non-fatal event of heart failure and two due to deaths, neither of which was considered related to the study drug. During the 18-month treatment period, there were two SAEs deemed related to vutrisiran by the study investigator, consisting of dyslipidemia and urinary tract infection. The two deaths and the two related SAEs were previously reported in the 9-month topline results. Treatment emergent AEs occurring in 10 percent or more patients included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia and dizziness; with the exception of pain in extremity and arthralgia, each of these events occurred at a similar or lower rate as compared with external placebo. Injection site reactions were reported in 5 patients (4.1 percent) and were all mild and transient. There were no hepatic safety concerns.

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 patients with ATTR amyloidosis (wild-type or hereditary) with cardiomyopathy. Patients were 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 endpoint of all-cause mortality and recurrent cardiovascular events at 30 months. 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. In August 2021, we announced full patient enrollment in the HELIOS-B study. Enrollment was completed significantly ahead of schedule, with 655 ATTR amyloidosis patients across 123 activated sites in 33 countries. Topline results from the HELIOS-B study are expected in early 2024.

Potential Opportunity in Stargardt Disease

Based on the data from the HELIOS-A Phase 3 study, we believe there may be a near term opportunity for vutrisiran as an investigational RNAi therapeutic for the potential treatment of Stargardt Disease. Stargardt Disease is a rare, inherited form of blindness caused by accumulation of toxic vitamin A metabolites in the retina which leads to central vision loss. It is a leading cause of blindness from inherited retinal diseases in children, and almost all people affected by this disease become legally blind as adults. Stargardt Disease is estimated to affect about 65,000 people in the U.S. and EU (incidence of approximately 1 in 8,000-10,000), with high unmet medical need and no approved treatments.

TTR functions as a transporter of vitamin A in the blood. It forms a complex with retinol binding protein, or RBP4, to deliver vitamin A to extrahepatic tissues, including the eye. In healthy individuals, the protein ABCA4 acts as a transporter for vitamin A in the eye, ensuring that toxic vitamin A metabolites do not accumulate in the retina. In contrast, patients with Stargardt Disease have an inherited defect in ABCA4. As a result, toxic vitamin A metabolites accumulate in the retina as lipofuscin, triggering degeneration of macular rods and cones, leading to central vision loss and eventually blindness in most patients.

We believe that RNAi-mediated serum TTR reduction with vutrisiran has the potential to reduce RBP4-mediated delivery of vitamin A to the eye and could prevent lipofuscin accumulation and resulting macular damage. Data from the HELIOS-A Phase 3 study of vutrisiran have demonstrated a high correlation between serum TTR reduction and vitamin A reduction, supporting the therapeutic hypothesis.

We plan to initiate a Phase 3 study in patients with Stargardt Disease in late 2022, following discussions with health agencies.

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, Canada, and marketing authorizations for GIVLAARI for the treatment of AHP in adults and adolescents in Japan, Argentina and Switzerland. We have also filed for regulatory approval for givosiran (the non-branded drug name for GIVLAARI) in Israel, Taiwan, and Colombia and additional regulatory filings are pending or planned in 2022 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.

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 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. In June 2021, we received marketing authorization approval for OXLUMO in Brazil for the treatment of PH1 in both children and adult patients, and regulatory filings in other territories are pending and additional filings are planned for 2022 and beyond.

PH1 is an ultra-rare 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. Renal damage is caused by a combination of tubular toxicity from oxalate, calcium oxalate deposition in the kidneys, and urinary obstruction by calcium oxalate stones. 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 PH1. In July 2021, we reported positive topline results from the ILLUMINATE-C study, and based on those positive results, in December 2021, we submitted a supplemental NDA to the FDA and Type II Filing Variation to the EMA to support label expansion for OXLUMO for the treatment of advanced PH1.

ILLUMINATE-C

ILLUMINATE-C is a single-arm, open-label, multinational Phase 3 study evaluating the safety and efficacy of lumasiran in PH1 patients of all ages with severe renal impairment (eGFR $\leq$ 45 mL/min/1.73m^2 or elevated serum creatinine for patients <12 months of age). The study is being conducted at 13 study sites across 10 countries around the world. 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 hemodialysis-dependent. The dosing regimen is based on weight with three monthly starting doses followed by ongoing monthly or quarterly doses. The primary efficacy endpoint for Cohort A was the percent change in plasma oxalate, or POx, from baseline to month six, and the primary endpoint for Cohort B was the percent change in pre-dialysis POx from baseline to month six. Key secondary endpoints are designed to evaluate additional measures of POx and changes in urinary oxalate, and quality of life assessments. Kidney function, frequency and mode of dialysis, frequency of kidney stone events, and measures of systemic oxalosis, including clinical manifestations will also be evaluated in the extension period of the study.

- *Efficacy and Safety Results:* At six months, treatment with lumasiran in Cohorts A and B, respectively, led to 33 percent and 42 percent mean reductions in POx and predialysis POx from baseline to month six. Reduction in POx was evident by month one and persisted through the end of the 6-month primary analysis period. Lumasiran also demonstrated positive results across secondary endpoints, including patients in Cohort B achieving substantial reductions in POx area under the curve 0-24h between dialysis sessions from baseline to month six, and lumasiran demonstrating consistent reductions across all measures of urinary oxalate in Cohort A. In addition, a similar magnitude of plasma glycolate increase, an exploratory endpoint in Cohorts A and B, was observed as compared to previously completed studies in patients with relatively preserved kidney function (ILLUMINATE-A and ILLUMINATE-B), suggesting similar pharmacodynamics of lumasiran regardless of kidney function. Mild and transient injection site reactions were the most common drug-related AE reported in 24 percent (5/21) of patients. There were no deaths and no serious or severe AEs related to lumasiran. Furthermore, there were no treatment discontinuations or study withdrawals.

In addition to our ILLUMINATE program, we are evaluating the safety and efficacy of lumasiran in patients with recurrent kidney stone disease in a proof-of-concept Phase 2 study which was initiated in December 2021. The Phase 2 trial is a randomized, double-blind, placebo-controlled study to evaluate the safety, efficacy, pharmacodynamics, and pharmacokinetics of lumasiran administered subcutaneously in patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels. The global, multicenter trial is expected to enroll 120 adults with a documented diagnosis of recurrent calcium oxalate kidney stone disease, based on two or more stone events within five years prior to screening, and whose 24-hour urinary oxalate levels are greater than the upper limit of normal. Study participants will be randomized 1:1:1 to receive either placebo or lumasiran at 567 mg or 284 mg on Day 1, Month 3, and Month 9 of a 15-Month double-blind treatment period that includes a six-month primary analysis period followed by a nine-month treatment extension period. The primary endpoint of the Phase 2 study is the percent change in 24-hour urinary oxalate after six months of treatment. Key secondary endpoints include the percentage of patients who achieve a 20 percent or greater reduction in 24-hour urinary oxalate and percent change in urinary calcium oxalate supersaturation after six months of treatment. Topline results are expected in mid-2023.

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) to lower low-density lipoprotein cholesterol (also known as "bad cholesterol" or LDL-C), and is the first RNAi therapeutic approved for a highly prevalent disease. Leqvio is a subcutaneously administered RNAi therapeutic targeting proprotein convertase subtilisin/kexin type 9, or PCSK9, to reduce LDL-C levels via an RNAi mechanism of action and could help improve outcomes for patients with ASCVD, a deadly form of cardiovascular disease. 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 2021, the FDA approved Leqvio as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD who require additional lowering of LDL-C. Leqvio has also been granted Orphan Drug Designation in the U.S. for the treatment of homozygous familial hypercholesterolemia, or HoFH. As of January 2022, Leqvio has been approved in more than 50 countries.

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 and approvals for Leqvio 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. This Phase 3 program represents the largest clinical program conducted to date for an investigational RNAi therapeutic program. Two additional Phase 3 cardiovascular outcomes trials, ORION-4 and the Novartis initiated VICTORION-2-PREVENT are currently ongoing.

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, in collaboration with our partner, Sanofi. 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 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 announced that it would resume fitusiran dosing in ongoing adolescent and adult clinical studies. Sanofi has since resumed fitusiran dosing in all ongoing studies 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 with additional lower doses, Sanofi expects that global regulatory submission timelines for the adult and adolescent studies will be delayed, subject to alignment with health authorities, and in October 2021, Sanofi announced that the potential filing date for fitusiran had been moved to 2024. Fitusiran has received both U.S. and EU Orphan Drug Designations for the treatment of hemophilia A and B.

In December 2021, Sanofi presented positive results from the ATLAS-A/B and ATLAS-INH Phase 3 studies of fitusiran.

ATLAS-A/B

ATLAS-A/B is a Phase 3 randomized, open-label study investigating the efficacy and safety of fitusiran in males ≥12 years with severe hemophilia A or B without inhibitors who had previously been treated with on-demand factor therapy. Study participants (n=120) were randomized 2:1 to receive either once-monthly 80mg subcutaneous fitusiran prophylaxis or on-demand factor therapy for bleeding episodes. The primary endpoint is annualized bleeding rate, or ABR.

- *Efficacy and Safety Results:* All key primary and secondary endpoints were met in ATLAS-A/B. Once-monthly 80mg subcutaneous fitusiran prophylaxis demonstrated a significant reduction in annualized bleeding rate, annualized spontaneous bleeding rate, and annualized joint bleeding rate (all ~90 percent) in people with severe hemophilia A or B without inhibitors compared with on demand treatment. This reduction in bleeding was associated with a meaningful improvement in health-related quality of life. Reported treatment emergent SAEs were generally consistent with previously identified risks of fitusiran. Treatment emergent SAEs in the fitusiran arm included cholelithiasis (two patients, 2.5 percent), cholecystitis, lower respiratory tract infection, and asthma (one patient each, 1.3 percent). In the fitusiran arm, two patients (2.5 percent) experienced Treatment emergent AEs that resulted in fitusiran discontinuation (cholecystitis and increased alanine aminotransferase). No treatment emergent AEs of thrombosis and no fatal treatment emergent AEs were reported.

ATLAS-INH

The ATLAS-INH study is a randomized, open-label Phase 3 study designed to evaluate the safety and efficacy of fitusiran in males ≥12 years with severe hemophilia A or B with inhibitors to factor VIII or IX. Study participants (n=57) receiving on-demand treatment with bypassing agents, or BPA, were randomized in a 2:1 ratio to receive once-monthly 80mg subcutaneous fitusiran prophylaxis or continue with on-demand BPA. The primary endpoint is ABR. Sanofi is currently investigating the efficacy and safety of fitusiran under an amended protocol which includes lower doses and an extended dosing regimen in all ongoing adult and adolescent studies.

- *Efficacy and Safety Results:* In ATLAS-INH, 80mg monthly subcutaneous fitusiran significantly reduced bleeding with a median ABR of zero and significant proportion of people with zero bleeds, resulting in a meaningful improvement in health-related quality of life. Reported treatment emergent SAEs were generally consistent with what is anticipated in an adult and adolescent population with severe hemophilia A or B with inhibitors, or with the previously identified risks of fitusiran. All treatment emergent SAEs were reported in one patient each; in the fitusiran prophylaxis arm these included events of device related infection, hematuria, spinal vascular disorder, subclavian vein thrombosis, thrombosis, acute cholecystitis, chronic cholecystitis and asymptomatic COVID-19. One patient (2.4%) in the fitusiran arm experienced treatment emergent AEs that resulted in study drug discontinuation (spinal vascular disorder and thrombosis). There were no fatal treatment emergent AEs reported.

In January 2018, we and Sanofi 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 has global rights to develop and commercialize fitusiran and any back-up products. The 2014 Sanofi 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 topline results from our Phase 2 clinical trial of cemdisiran in patients with IgA nephropathy are expected in early 2022. Cemdisiran is also being evaluated by our partner, Regeneron, in combination with Regeneron's pozelimab (REGN3918), an anti-C5 monoclonal antibody. In late 2021,

Regeneron initiated a Phase 3 study of cemdisiran and pozelimab combination in myasthenia gravis, in addition to multiple Phase 2 studies and a Phase 3 study in paroxysmal nocturnal hemoglobinuria.

Zilebesiran (formerly ALN-AGT) — Hypertension

Zilebesiran is an investigational, subcutaneously administered RNAi therapeutic targeting angiotensinogen, or AGT, in development for the treatment of hypertension in high unmet need populations. AGT is the most upstream precursor in the renin-angiotensin-aldosterone system, a cascade which has a demonstrated role in blood pressure regulation and its inhibition has well-established anti-hypertensive effects. Zilebesiran inhibits the synthesis of AGT in the liver, potentially leading to durable reductions in AGT protein and ultimately, in the vasoconstrictor angiotensin II.

Hypertension is a complex multifactorial disease clinically defined by most major guidelines as a systolic blood pressure of above 140 mm Hg and/or a diastolic blood pressure greater than 90 mm Hg. More than one billion people worldwide live with hypertension. In the U.S. alone, approximately 47 percent of adults live with hypertension, with more than half of patients on medication remaining above the blood pressure target level. Despite the availability of anti-hypertensive medications, there remains a significant unmet medical need, especially given the poor rates of adherence to existing daily oral medications and daily peak and trough effects, resulting in inconsistent blood pressure control and an increased risk for stroke, heart attack and premature death. In particular, there are a number of high unmet need settings where novel approaches to hypertension warrant additional development focus, including patients with poor medication adherence, difficult-to-treat and resistant hypertension, and in patients with high cardiovascular risk.

In November 2021, we reported positive interim data from the ongoing Phase 1 study of zilebesiran, and also initiated the KARDIA Phase 2 clinical studies for zilebesiran. KARDIA-1 is designed to evaluate zilebesiran as a monotherapy across different doses administered quarterly and biannually, whereas KARDIA-2 will evaluate the safety and efficacy of zilebesiran administered biannually as a concomitant therapy in patients whose blood pressure is not adequately controlled by standard of care antihypertensive medications.

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, in 2021, Vir continued to progress a Phase 2 combination trial of VIR-2218 with pegylated interferon-alpha to evaluate the potential for the combination to result in a functional cure for HBV. VIR-2218 is also being explored in additional clinical trials with collaborators of Vir. Vir plans to report additional results from the Phase 2 program in middle and late 2022.

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 2021, we advanced ALN-HSD into Part B of the ongoing Phase 1 study in patients with NASH.

ALN-APP – Alzheimer's Disease and Cerebral Amyloid Angiopathy

ALN-APP is an investigational, intrathecally administered RNAi therapeutic targeting amyloid precursor protein, or APP, in development in collaboration with Regeneron for the treatment of Alzheimer's disease, or AD, and cerebral amyloid angiopathy. Genetic mutations that increase production of APP or alter its cleavage cause early-onset AD, early-onset CAA, or both. ALN-APP is designed to decrease APP mRNA in the CNS, to decrease synthesis of APP protein and all downstream intracellular and extracellular APP-derived cleavage products, including amyloid beta (Aβ). Reducing APP protein production is expected to reduce the secretion of Aβ peptides that aggregate into extracellular amyloid deposits and reduce the intraneuronal APP cleavage products that trigger the formation of neurofibrillary tangles and cause neuronal dysfunction in AD. ALN-APP is the first program utilizing our C16 conjugate technology, which enables enhanced delivery to cells in the CNS.

In December 2021, we announced submission of our CTA to The Medicines and Healthcare Products Regulatory Agency, or MHRA, in the United Kingdom to initiate a Phase 1 study of ALN-APP, with a plan to initiate the Phase 1 study in patients with early-onset AD in early 2022, upon obtaining MHRA approval. We expect to report topline Phase 1 results in late 2022.

ALN-XDH - Gout

ALN-XDH is an investigational, subcutaneously administered RNAi therapeutic targeting xanthine dehydrogenase, or XDH, in development for the treatment of gout. Reducing XDH with an RNAi therapeutic is expected to result in potent urate lowering, essential in preventing gout-associated flares and managing the disease. ALN-XDH utilizes our ESC+ GalNAc-conjugate technology, which enables subcutaneous dosing with increased selectivity and a wide therapeutic index.

In December 2021, we announced submission of our CTA to the MHRA in the United Kingdom to initiate a Phase 1/2 study of ALN-XDH in healthy volunteers and in patients with gout in early 2022, upon obtaining MHRA approval. We expect to report topline Phase 1 results in late 2022.

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 two to four investigational new drug applications, or INDs, or CTAs from our organic product engine during 2022. We also intend to continue to build on our progress with extrahepatic delivery during 2022, advancing our eye and CNS programs under our collaboration with Regeneron, as well as continuing to advance other extrahepatic delivery initiatives.

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. We are also advancing multiple other programs with Regeneron.

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, which we further expanded in April 2020 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, and potentially a third mutually selected host factor target. In July 2021, we notified Vir that we elected to discontinue ALN-COV, in development for the treatment of COVID-19, and all other COVID-19 research and development activities, based on a portfolio prioritization in view of the availability of highly effective vaccines and alternative treatment options. Following such discontinuation of COVID-19 related activities, we have no further obligations to work on the COVID-related targets and Vir will have no further rights to such targets under our exclusive licensing agreement.

With respect to our Genetic Medicine pipeline, we formed a broad strategic alliance with Sanofi in 2014. In January 2018, we and Sanofi 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 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 agreed to further amend the 2014 Sanofi

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 will continue to evaluate and explore partnership opportunities through collaboration and licensing arrangements, and may enter into new collaborations to advance certain products or disease areas. For example, in January 2022, we announced that we and Novartis agreed to collaborate on the discovery and development of an siRNA-based targeted therapy to restore functional liver cells in patients with end-stage liver diseases.

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. For example, in 2021, we entered into a license and collaboration agreement with PeptiDream to discover and develop peptide-siRNA conjugates leveraging PeptiDream's proprietary Peptide Discovery Platform System technology.

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 3 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. We are also advancing multiple other programs with Regeneron.

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. In January 2014, we entered into a global, strategic collaboration with Sanofi to discover, develop and commercialize RNAi therapeutics as Genetic Medicines to treat orphan diseases, referred to as the 2014 Sanofi collaboration. The 2014 Sanofi collaboration superseded and replaced the previous collaboration between us and Sanofi 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 entered into an amendment to our 2014 Sanofi collaboration. In connection and simultaneously with entering into the 2018 amendment to the 2014 Sanofi collaboration, we and Sanofi 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 has the exclusive right to pursue the further global development and commercialization of fitusiran and any back-up products. Under the 2018 amendment and the Exclusive TTR License, Sanofi 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 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 described below made no changes to the terms described in clauses (i)-(iii) above, which remain in full force and effect.

In April 2019, we and Sanofi agreed to further amend the 2014 Sanofi 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. 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, in each case by Sanofi, its affiliates and its sublicensees. 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. Thereafter, Sanofi 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.

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. In December 2021, Leqvio was approved by the FDA for the treatment of adults with HeFH or clinical ASCVD as an adjunct to diet and maximally tolerated dose of statin. 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, or the Vir 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 were 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 were responsible for all pre-clinical development costs incurred under such plan. In July 2021, we notified Vir that we elected to discontinue ALN-COV, in development for the treatment of COVID-19, and all other COVID-19 research and development activities, based on a portfolio prioritization in view of the availability of highly effective vaccines and alternative treatment options. Following such discontinuation of COVID-19 related activities, we have no further obligations to work on the COVID-related targets and Vir will have no further rights to such targets under our exclusive licensing agreement. 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 agreed to 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 zilebesiran (formerly ALN-AGT) pursuant to the funding agreement finalized in August 2020. In November 2021, Blackstone elected to opt-in to Phase 2 clinical trial funding of zilebesiran, committing to fund, upon meeting certain patient enrollment thresholds, up to $26.0 million. 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, including its ongoing financial and accounting impact on our business.

Other Strategic License Agreements

Dicerna Pharmaceuticals, Inc. In April 2020, we and Dicerna (acquired by Novo Nordisk in December 2021) 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 belcesiran (formerly 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.

PeptiDream, Inc. In July 2021, we entered into a license and collaboration agreement with PeptiDream to discover and develop peptide-siRNA conjugates to create multiple opportunities to deliver RNAi therapeutics to tissues outside the liver. Through this collaboration, the companies will collaborate to select and optimize peptides for targeted delivery of small siRNA molecules to a wide range of cell types and tissues via specific interactions with receptors expressed on the target cells. Under the terms of the alliance, we will select a set of receptors for PeptiDream's peptide discovery platform. PeptiDream will select, optimize, and synthesize peptides for each receptor. We will then generate peptide-siRNA conjugates and perform in vitro and in vivo studies to support final peptide selection. For more information regarding the collaboration agreement with PeptiDream, 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.

Novartis AG. In January 2022, we announced that we and Novartis, entered into a collaboration and license agreement, referred to as the Novartis License Agreement, pursuant to which we granted to Novartis an exclusive, worldwide license to develop, manufacture and commercialize siRNAs targeting end-stage liver disease, potentially leading to the development of a treatment designed to promote the regrowth of functional liver cells and to provide an alternative to transplantation for patients with liver failure. Under the terms of the collaboration, we will develop and test potential siRNAs using target-specific assays developed by Novartis. Upon identification of a lead candidate, further development and clinical research will be conducted by Novartis. Pursuant to the Novartis License Agreement, we received an upfront fee, and may also receive milestone payments upon the achievement of certain development, regulatory and commercial milestones, as well as tiered royalties on the net sales of licensed products ranging from high-single-digit to sub-teen double-digit percentages. For more information regarding the Novartis License 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.

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 products marketed by us 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 and ODE until November 23, 2027. 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® and the ONPATTRO logo, GIVLAARI® and the GIVLAARI logo and OXLUMO® and the OXLUMO logo.

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 Marina Biotech, Inc., or Marina, Arrowhead Pharmaceuticals, Inc., or Arrowhead, and its collaborators Takeda Pharmaceutical Company Ltd., or Takeda, Janssen Pharmaceutics, Inc. or Janssen, Horizon Therapeutics PLC, or Horizon, GlaxoSmithKline PLC, or GSK, and Amgen Inc., or Amgen, Quark Pharmaceuticals, Inc., or Quark, F. Hoffmann-La Roche Ltd, or Roche, Silence Therapeutics plc, or Silence, and its collaborators, AstraZeneca plc, or AstraZeneca, Jiangsu Hansoh Pharmaceuticals Group Co., and Mallinckrodt plc, Arbutus Biopharma Corp., or Arbutus, Sylentis, S.A.U., or Sylentis, Novo Nordisk and its collaborators, Boehringer Ingelheim, AstraZeneca plc, or AstraZeneca, 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, BioPath Holding Inc., Arcturus Therapeutics, Inc., or Arcturus, and Ascletis Pharma Inc. 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, and InteRNA Technologies B.V.

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, Novartis and Bayer AG, and several 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. We believe that the following approved drugs could compete with ONPATTRO and, if approved, vutrisiran, for the treatment of the polyneuropathy of hATTR amyloidosis in adults and for the treatment of ATTR amyloidosis with cardiomyopathy if APOLLO-B and/or HELIOS-B is positive and patisiran and/or vutrisiran, respectively, are approved for that indication:

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	Anti-sense oligonucleotide, or 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)

Several investigational drugs also exist, in varying stages of clinical development, for ATTR amyloidosis. We believe that the following drug candidates, if approved, could compete with ONPATTRO and, if approved, vutrisiran, for the treatment of the polyneuropathy of hATTR amyloidosis in adults and for the treatment of ATTR amyloidosis with cardiomyopathy if APOLLO-B and/or HELIOS-B is positive and patisiran and/or vutrisiran, respectively, are approved for that indication:

Drug	Company	Drug Description	Phase	Administration/Dosing
Eplontersen (IONIS-TTR-L_{Rx})	Ionis & AstraZeneca	ASO to reduce production of TTR Protein	Phase 3	Monthly subcutaneous injection (SC)
Acoramidis (AG10)	BridgeBio Pharma, Inc.	Small molecule drug to stabilize TTR protein	Phase 3	Twice daily oral dose
PRX004	Novo Nordisk	mAb to clear amyloid deposits	Phase 2/3	Intravenous (IV) infusion every four weeks
NI006	Neurimmune AG & AstraZeneca	mAB to clear amyloid deposits	Phase 1	Intravenous (IV) infusion
NTLA-2001	Intellia Therapeutics, Inc. & Regeneron	CRISPR/Cas9 gene therapy	Phase 1	One-time intravenous (IV) infusion

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 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	Novo Nordisk	siRNA to reduce production of LDHA enzyme	Phase 2 (pivotal)	SC with monthly dosing
BBP-711	BridgeBio Pharma, Inc.	GO inhibitor	Phase 1	Oral
Oxabact OC5	OxThera AB	Anaerobic bacteria that metabolize oxalate in the gut	Phase 3 (failed to meet statistical significance)	Twice daily oral dose
Stiripentol	Biocodex SA	GABA reuptake inhibitor	Phase 2	Oral
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 for the treatment of adults with hypercholesterolemia or mixed dyslipidemia and in the U.S. for the treatment of adults with HeFH or clinical ASCVD as an adjunct to diet and maximally tolerated dose of statin, 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 and other cholesterol lowering agents 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	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
Evkeeza (evinacumab)	Regeneron	Anti-ANGPTL3 mAb for hypercholesterolemia	Approved in HoFH	SC
ARO-ANG3	Arrowhead	siRNA targeting ANGPTL3	Phase 2	SC
Vupanorsen	Ionis / Pfizer	ASO therapy to reduce levels of ANGPTL3	Phase 2b	SC
LIB-003	LIB Therapeutics	Recombinant protein therapeutic	Phase 3	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
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/PF06838435 (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 the FDA's 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 applicable federal regulations and requirements, including in some cases the FDA's good laboratory practice requirements and the Animal Welfare Act. 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. 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 may also 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 2022, the application fee for each NDA requiring clinical data is approximately $3.1 million. The PDUFA also imposes an annual program fee for each approved prescription drug, which has been set at approximately $369,000 for fiscal year 2022. 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 the FDA's 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 may refer the application 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's 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.

Post-Approval Regulation

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 approval 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 will 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 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 for the treatment of the polyneuropathy of hATTR amyloidosis in adults, 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

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 healthcare 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. Factors payors consider in determining reimbursement are based on whether the product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

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 healthcare 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.

Healthcare 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 healthcare-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, healthcare products and services reimbursed by a federal healthcare 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 healthcare programs. Exclusion of a manufacturer would preclude any federal healthcare 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 healthcare 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 healthcare 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 healthcare 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 healthcare 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.

As described above, we maintain a global compliance program designed to support the execution of our business strategy and operations in compliance with these laws.

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.

Our present and future business has been and will continue to be subject to various other laws and regulations. Various laws, regulations and recommendations relating to safe working conditions, laboratory practices, the experimental use of animals, and the purchase, storage, movement, import, export and use and disposal of hazardous or potentially hazardous substances are or may be applicable to our activities. As noted above, the extent of government regulation, which might result from future legislation or administrative action, cannot accurately be predicted.

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 EU Regulation on Clinical Trials, which became applicable on January 31, 2022, there is 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.

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 will 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 market exclusivity period may be extended to three years if during the first eight years of the product's authorisation, 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 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 or where no satisfactory method of diagnosis, prevention or treatment of such condition exists. 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, givosiran, approved in the EU in March 2020, lumasiran, approved in the EU in November 2020, as well as vutrisiran 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.

Regulation of New Drug Compounds in Other Jurisdictions

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 2021, 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 2022, 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 additional 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.

In 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.

During 2020, we completed construction and qualification of our cGMP manufacturing facility in Norton, Massachusetts where we currently manufacture drug substance for clinical programs and, eventually, intend to manufacture drug substance for 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 Norton 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 company's journey: launching our RNAi therapeutics, based on regulatory approvals, to reach eligible patients in need. 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 with broad industry experience 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 granted MDCO, which was acquired by Novartis in January 2020, global rights to develop and commercialize; and
- For fitusiran, Sanofi has global rights to develop and commercialize fitusiran and any back-ups as a result of the 2018 amendment to the Sanofi 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 strategy to make ONPATTRO, GIVLAARI, OXLUMO and future orphan products successful, including through efforts to increase awareness and diagnosis. In addition, as part of our planned transition to a top five biotech by the end of 2025 and consistent with our *Alnylam P*^{5}*x25* strategy, we are now advancing RNAi therapeutics beyond rare diseases into prevalent disease opportunities. With the approval of Leqvio, the first RNAi therapeutic approved for a common disease, we believe the RNAi therapeutic profile supports the potential for expansion to prevalent diseases, including addressing many unmet needs in common disease settings such as hypertension, NASH, gout and diabetes. We believe we are establishing a global commercial organization and infrastructure to successfully support an expansion to prevalent diseases.

We have a proactive market access strategy that includes entering into value-based agreements, or VBAs, with commercial payers in the U.S. and certain state Medicaid programs. As of the beginning of 2022, we have completed at least 43 VBAs with multiple commercial payers, including 19 for ONPATTRO, 13 for GIVLAARI, and 11 for OXLUMO. In our VBAs for GIVLAARI we introduced a Prevalence Based Adjustment that provides for a rebate to be paid if the number of patients identified within a plan population exceeds the expected disease prevalence, to address an unknown that exists in the context of an ultra-rare disease. For OXLUMO, we established a new VBA component called a Patient Need Adjustment with the effect of providing payers with greater budget certainty for medicines administered across a broad range of patient age groups by paying a rebate if the average number of vials utilized by a plan member exceeds an established threshold. Discussions with additional 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, assuming successful development and regulatory approval. With respect to commercially approved products, throughout 2021, we continued to build our commercial capabilities, including establishing 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 and enhance 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, GIVLAARI and OXLUMO to also support 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, GIVLAARI and OXLUMO.

Medical Affairs

Our Global Medical Affairs organization advances our efforts through stakeholder engagement, data dissemination, and healthcare professional education, ultimately enabling diagnosis and improving patient care. This begins with our efforts to engage patient groups and communities, improve disease awareness and increase patient diagnosis, including through support for independent third party genetic testing programs like Alnylam Act. With a scalable framework in these capabilities, we believe our Global Medical Affairs organization is well positioned to expand to prevalent diseases.

Human Capital Management

As of December 31, 2021, we employed 1,665 full-time employees, of whom approximately 1,290 were employed in the U.S. and approximately 375 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 2021, we enhanced our capabilities by adding 212 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, compliance, legal, clinical development and operations, research, medical affairs, manufacturing, and general and administrative functions. We expect to continue to add additional employees in 2022, with a focus on further enhancing our capabilities and increasing our capacities in these areas, in particular our manufacturing, commercial and compliance teams, 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.

SUMMARY OF MATERIAL RISKS ASSOCIATED WITH OUR BUSINESS

Our business is subject to numerous risks and uncertainties, discussed in more detail in the following section. These risks include, among others, the following key risks:

Business Related Risks – Risks Related to Our Financial Results

- The current pandemic of COVID-19 and its variants and the future outbreak of other highly infectious or contagious diseases, could continue to have an adverse impact on our business, financial condition and results of operations, including our commercial operations and sales, clinical trials and pre-clinical studies, and could impact other areas of our business as well.
- The marketing and sale of ONPATTRO, GIVLAARI, OXLUMO or any future products, including vutrisiran, may be unsuccessful or less successful than anticipated and we may be unable to expand the indication for ONPATTRO, or, if approved, vutrisiran.
- 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, 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 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 certain of our 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 recently underwent our first CEO succession. Any leadership transition carries with it disruption risks that could have a negative impact on the execution of our *Alnylam P^{5}x25* strategy. These risks include our ability to attract and retain qualified employees.
- We may have difficulty expanding our operations successfully as we continue our evolution from a U.S.- and Europe-based company primarily involved in discovery, pre-clinical testing and clinical development into a global company that develops and commercializes multiple drugs in multiple geographies including Asia, Latin America and the Middle East.
- We may experience computer system failures or unauthorized or inappropriate use of or access to our information systems or those of our contractors or collaborators, potentially resulting in substantial loss of data, business interruption or other harm.

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 are a multi-product commercial company and expect to continue to invest significant financial and management resources to continue to scale our marketing, sales, market access and distribution capabilities and further establish our global commercial and compliance infrastructure, and our commercial efforts may not be successful.
- The patient populations suffering from hATTR amyloidosis with polyneuropathy, AHP, and 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, including in connection with the ongoing DOJ investigation.
- 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, as well as from companies utilizing emerging technologies, including gene therapy and gene editing.

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.

Risks Related to Our Business

Risks Related to Our Financial Results

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

The novel coronavirus identified in late 2019, SARS-CoV-2, which causes the disease known as COVID-19, has led to an ongoing global pandemic that continues to evolve and the ultimate impact of this pandemic remains highly uncertain. To date, the COVID-19 pandemic has led to the implementation of various responses, including government-imposed quarantines, travel restrictions and other public health safety measures. COVID-19 has and may 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, the effectiveness of vaccination and booster vaccination campaigns, among others. The continued development and fluidity of the COVID-19 pandemic precludes any prediction as to its full impact on our business.

In response to the spread of COVID-19, we took, and have continued to take, both temporary and ongoing 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 in early March 2020 for nearly all employees who were able to perform their duties remotely. In addition, in October 2021, we implemented a mandatory vaccination policy requiring all U.S. employees and contractors to be fully vaccinated, subject to certain medical and religious accommodations. Where and to the extent permitted to be open under local regulations, our office sites are operational with appropriate safety precautions based on COVID-19 vaccination rates and local guidance, and in October 2021, we formally re-opened our U.S. offices to those employees who have been fully vaccinated. Working arrangements for many of our employees differ from the arrangements before the COVID-19 pandemic, and we expect a number of employees will continue to work in a remote capacity or a hybrid of in-person and remote work. We may face several challenges or disruptions during our return to the workplace transition, including re-integration challenges for our employees, and our hybrid of in-person and remote work option 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. We cannot predict when certain restrictions that are in place to protect our employees can be further reduced or will no longer be needed. 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 the pandemic continues, and if conditions worsen or if the duration of the pandemic extends significantly, we may experience disruptions that could severely impact our business and operations, including our ability to successfully commercialize our approved products, and we may not be able to meet expectations with respect to commercial sales. 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. Business interruptions from the current or future pandemics, including staffing shortages, raw material or other supply chain 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 are 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 2022. 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. 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, when foreign and domestic inspections of facilities were largely placed on hold, the FDA has been working to resume routine surveillance, bioresearch monitoring and pre-approval inspections on a prioritized basis. Since April 2021, the FDA has conducted limited inspections and employed remote interactive evaluations, using risk management methods, to meet user fee commitments and goal dates. Ongoing travel restrictions and other uncertainties continue to impact oversight operations both domestic and abroad and it is unclear when standard operational levels will resume. The FDA is continuing to complete mission-critical work, prioritize other higher-tiered inspectional needs (e.g., for-cause inspections), and carry out surveillance inspections using risk-based approaches. 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, and the FDA does not determine a remote interactive evaluation to be adequate, the FDA has stated that it generally intends to issue, depending on the circumstances, a complete response letter or 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. The FDA ultimately approved Novartis' NDA in December 2021. 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 ongoing 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 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 CMOs due to staffing shortages, production slowdowns, raw material or other supply shortages, or stoppages and disruptions in delivery systems.

These and other factors arising from the COVID-19 pandemic could worsen in countries with higher infection rates and case counts, 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 marketing and sale of ONPATTRO, GIVLAARI, OXLUMO or any future products, including vutrisiran, may be less successful than anticipated, and we may be unable to expand the indication for ONPATTRO, or, if approved, vutrisiran.

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 has since received approval in several additional territories, and in 2020, the FDA and EMA approved our third product, OXLUMO, which received additional regulatory approvals in 2021. We also have several product candidates in late-stage clinical development, including vutrisiran, which is currently under review by the FDA, and has a PDUFA date of April 14, 2022, as well as other agencies. While we have commercially launched three

products, we cannot predict whether we will successfully overcome many of the risks and uncertainties encountered by companies commercializing products in the biopharmaceutical industry. To execute our business plan of building a profitable, top five biotech company over the next 5 years and achieving our *Alnylam P[5]x25* 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 liver, CNS, eye, lung and muscle;
- successfully execute our leadership succession plan;
- 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 the objectives set forth above, 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 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, 2021, we had an accumulated deficit of 5.44 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 2022 and beyond, we may never attain profitability or positive cash flow from operations. For the year ended December 31, 2021, we recognized $662.1 million in net product revenues from sales of ONPATTRO, GIVLAARI and OXLUMO. While our full year operating loss for 2021 and 2020 each improved relative to the prior year, marking 2019 as our peak operating loss year, we expect to continue to incur annual 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 self-sustainability 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, including Novartis and Regeneron. We cannot be certain that we will be able to maintain our existing alliances, secure and maintain new alliances, 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. Moreover, we cannot be certain that our partners, including Novartis, will continue to successfully execute their obligations under our alliance agreements and generate additional revenues for us.

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 continued platform innovation, 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 generate revenues that are significant enough to achieve profitability and, 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, including programs in both rare and prevalent diseases 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 commercialized by our partner, Novartis;
- our ability to maintain and establish additional collaborative arrangements and/or new business initiatives;
- the potential for improved product profiles to emerge from our new technologies and our ability to successfully advance our delivery efforts in extrahepatic tissues;
- 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 and government investigations, arising in the course of our business activities and our ability to prevail or reach a satisfactory result in any such legal disputes and investigations;
- 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 provided for a senior secured delayed draw term loan facility, funded in three tranches, or Term Loans, each tranche as 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 zilebesiran (formerly 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 zilebesiran 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 and the second and third tranches of $250.0 million each, were drawn under the Credit Agreement, as amended, in June and December 2021, respectively. 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 default on our Term Loans, 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 and filed a registration statement on June 5, 2020. 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 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 inspection-related conditions at a third party manufacturing facility, delaying the potential approval and launch of Leqvio in the U.S., as well as payment of an associated approval milestone and potential royalties. While Leqvio was granted marketing authorization by the EC in Europe in December 2020, and was approved by the FDA in December 2021, any negative impact to future royalty payments and commercial milestone payments 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 may continue to do so in the future. Our operating results may fluctuate due to the impact of the COVID-19 and related variants 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 combined product sales, collaboration and royalty revenues, and GAAP and 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 revenues and/or 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, 2021, we had $2.44 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 foreign currency exchange rates could have a material adverse effect on our operating results.

Our revenue from outside of the U.S. will increase as our products, whether commercialized by us or our collaborators, gain marketing approval in such jurisdictions. Our primary foreign currency exposure relates to movements in the Japanese yen, Euro and British pound. If the U.S. dollar weakens against a specific foreign currency, our revenues will increase, having a positive impact on net income, but our overall expenses will increase, having a negative impact. Conversely, if the U.S. dollar strengthens against a specific foreign currency, our revenues will decrease, having a negative impact on net income, but our overall expenses will decrease, having a positive impact. Therefore, significant changes in foreign exchange rates can impact our operating results and financial condition.

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

Our business is subject to numerous international, federal, state, and other governmental laws, rules, and regulations that may adversely affect our operating results, including, taxation and tax policy changes, tax rate changes, new tax laws, or revised tax law interpretations, which individually or in combination may cause our effective tax rate to increase. In the U.S., the rules dealing with federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations.

Additionally, the Organization for Economic Co-operation and Development, or OECD, the EC, and individual taxing jurisdictions where we and our affiliates do business have recently focused on issues related to the taxation of multinational corporations. The OECD has released its comprehensive plan to create an agreed set of international rules for fighting base erosion and profit shifting. In addition, the OECD, the EC and individual countries 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 formed in 2014, Sanofi 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. In April 2020, we entered into a development and commercialization collaboration with Dicerna (which was acquired by Novo Nordisk in December 2021) 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 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 inspection-related conditions at a third party manufacturing facility. While Leqvio was approved by the FDA in December 2021, the resolution of the complete response letter resulted in a delay in the payment of an approval milestone and potential U.S. royalties. 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 demonstrate improved product profiles from our new technologies, including our IKARIA and GEMINI platforms, our ability to successfully demonstrate proof-of-concept for our technology in humans in certain tissues or disease areas, including our alternative conjugate approach for delivering CNS or ocular product candidates or other extrahepatic approaches, 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 serious adverse event, or 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 (acquired by Novo Nordisk) and Sanofi. 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 Novartis at any time upon four months' prior written notice, provided if the agreement is terminated by Novartis for convenience, Novartis must 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 or disputes with Novartis regarding each party's rights and obligations under 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 manufacture drug substance for clinical and, eventually, will manufacture for commercial use. In December 2020, we began cGMP operations, and we believe this facility will enable us to initiate manufacturing for multiple 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. 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, 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. In response to the COVID-19 pandemic, in March 2020, the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, was enacted in March 2020, and requires that manufacturers 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, as a result of COVID-19 or otherwise, our results could be materially impacted. To date, three vaccines for COVID-19 have received Emergency Use Authorization by the FDA and two of those have since received marketing approval. Additional vaccines may be authorized or approved in the future. 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.

In developing 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. 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, 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 our commercial products and clinical candidates, and our dependence on our own facility, any delay in supply caused by the COVID-19 pandemic 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.

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.

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 PMDA in Japan or comparable foreign regulatory authorities may require us to take additional action or perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority in the future, such regulatory authority will determine that any of our clinical trials comply with GCP regulations.

If our third-party service providers cannot adequately and timely fulfill their obligations to us 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, in particular following our recent leadership transition, 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. We recently underwent our first leadership transition, and we believe our current management team is well-positioned to execute our strategy. Nonetheless, this recent leadership transition may be viewed negatively by employees, investors and/or our strategic partners. Moreover, attrition associated with this transition could significantly delay or prevent the achievement of product development and commercialization, and other business objectives, and adversely impact our stock price. 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*^{5}*x25* 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 three products, which we have launched in multiple geographies globally, and we continue to expand the reach of these products with additional regulatory filings and launches. In addition, we have a fourth product under review by regulatory authorities.

We have grown our workforce significantly over the last five years and anticipate continuing to hire additional employees globally in the future as we focus on the commercialization of ONPATTRO, GIVLAARI and OXLUMO, preparing for the potential launch of vutrisiran and achieving our *Alnylam P*^{5}*x25* 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, ethics and compliance functions, 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 use of social media presents risks and challenges.

Social media is 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 adverse event, or 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.

The pervasiveness of cybersecurity incidents in general and the risks of cyber-crime are complex and continue to evolve. Although we are making significant efforts to maintain the security and integrity of our information systems and are exploring various measures to manage the risk of a security breach or disruption, there can be no assurance that our security efforts and

measures will be effective or that attempted security breaches or disruptions would not be successful or damaging. 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.

Our business and operations may be negatively impacted by the United Kingdom's withdrawal from the EU.

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 an EU-UK Trade and Cooperation Agreement, or TCA, which became provisionally applicable on January 1, 2021 and has been formally applicable since May 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework will continue to apply in Northern Ireland). The regulatory regime in Great Britain therefore currently aligns with EU regulations, however it is possible that these regimes will diverge in future now that Great Britain's regulatory system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation. It remains to be seen how Brexit will impact regulatory requirements for medicinal products and devices in the UK in the long-term.

Since the expiry of the Transition Period, Great Britain is no longer covered by centralized marketing authorizations (under the Northern Ireland Protocol, centralized marketing authorizations will continue to be recognized in Northern Ireland). For a period of two years from January 1, 2021, the MHRA, the UK medicines regulator, may rely on a decision taken by the EC on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a new Great Britain marketing authorization. A separate application will, however, still be required. Any new divergent regulations in Great Britain and the EU 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. Any of these longer-term effects of Brexit, and others we cannot anticipate, could negatively impact our business and results of operations.

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 in patients with hATTR amyloidosis with polyneuropathy, we submitted an NDA for vutrisiran with the FDA in April 2021, which was accepted by the FDA. The FDA has set an action date of April 14, 2022 under PDUFA, and indicated that they were not currently planning an advisory committee meeting as part of the NDA review. In September 2021, we presented additional 9-month data from the HELIOS-A Phase 3 study of vutrisiran, and submitted an MAA in the EU with the EMA. Further, in January 2022, we reported positive full results for 18-month endpoints and safety from the HELIOS-A Phase 3 study of vutrisiran. We are also conducting additional Phase 3 trials of vutrisiran and patisiran in ATTR patients with cardiomyopathy. However, we may not be able to further advance these 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 or late stage clinical trials of a product candidate may not predict the results that will be obtained in subsequent subjects or in subsequent human clinical trials of that product candidate or any other product candidate. For example, we are conducting the APOLLO-B and HELIOS-B Phase 3 clinical trials of patisiran and vutrisiran, respectively, which are investigating the potential of patisiran and vutrisiran to treat the cardiac manifestations of disease in patients with ATTR amyloidosis with cardiomyopathy. While both patisiran and vutrisiran have demonstrated positive results in patients with hATTR amyloidosis with polyneuropathy, we cannot be certain that the results from APOLLO-B and/or HELIOS-B will be positive or support approval of patisiran and/or vutrisiran for the treatment of patients with ATTR amyloidosis with cardiomyopathy. 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, including with respect to patisiran and/or vutrisiran, 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 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 regulators, patients restarted on fitusiran under amended protocols in ongoing adolescent and adult clinical studies. In October 2021, Sanofi announced that a potential filing date for fitusiran has been moved to 2024 due to the introduction of a lower dose cohort in the ongoing phase 3 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'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 and increased costs 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. During the COVID-19 public health emergency, the FDA has worked to ensure timely reviews of applications for medical products in line with its user fee performance goals and conduct mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. 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 ongoing COVID-19 pandemic and travel restrictions the FDA is unable to complete such required inspections during the review period. During the COVID-19 public health emergency, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. 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. In July 2021, Novartis announced that the resubmission to the FDA of the inclisiran NDA to address the complete response letter was filed, and the FDA approved Leqvio (which is the trade name under which inclisiran will be marketed in the U.S.) in December 2021. The delay in the approval of Leqvio resulted in delayed milestone and royalty revenue to us. Any similar interruption or delay by the FDA, EMA or comparable foreign regulatory agency in light of the COVID-19 pandemic could have a material adverse effect on our efforts to obtain regulatory approval for our product candidates, including vutrisiran, 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 Risk Evaluation and Mitigation Strategy, or 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, as well as facilities at 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 this material 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.

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. In April 2021, we received a subpoena from the U.S. Department of Justice, U.S. Attorney's Office for the District of Massachusetts, requiring production of documents pertaining to our marketing and promotion of ONPATTRO (patisiran) in the U.S. We are cooperating with the U.S. Attorney's Office and producing documents in response to the subpoena. Current and former officers and employees also have received subpoenas in connection with the preservation and production of related materials. Given the ongoing nature of the investigation, it is possible that the U.S. Attorney's Office for the District of Massachusetts or other government entities may request other information from, or issue other subpoenas, findings or similar documents to, us, our related entities and their respective directors, officers and employees. If we are found to have improperly marketed or promoted ONPATTRO in connection with such subpoenas, we may be subject to a broad range of civil, administrative and criminal penalties, including injunctive relief related to ONPATTRO promotional activities, substantial fines or penalties, and other legal or equitable sanctions. Any adverse decision, finding, allegation, or exercise of enforcement or regulatory discretion could harm our business, prospects, operating results, and financial condition. Other internal or government investigations or legal or regulatory proceedings, including lawsuits brought by private litigants, may also follow as a consequence.

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.

As described above we remain focused on our global compliance program, which is designed to support the execution of these programs and activities in compliance with applicable laws.

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 Ionis in several countries, which is administered subcutaneously, or tafamidis, marketed by Pfizer Inc., or 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 a multi-product commercial company and expect to continue to invest significant financial and management resources to continue to build our marketing, sales, market access and distribution capabilities and further establish our global infrastructure. Even if we successfully scale our commercial capabilities, the market may not be receptive to our commercial products.

Having received our first product approval only four years ago, we 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 in major markets. Accordingly, we have developed internal marketing, sales, market access and distribution capabilities as part of our core product strategy initially in the U.S., Europe and Japan, 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:

- scaling and retaining our global sales, marketing and administrative infrastructure and capabilities;
- hiring, training, managing and supervising our personnel worldwide;
- the cost of further developing, 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, including vutrisiran, 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 in the future 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.

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 40 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 the performance of our approved products in real-world use to financial terms. Partnering with payers on these agreements is also intended to provide more certainty to them for their investment and help accelerate coverage decisions for patients. If the payment we receive 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 7.0% 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.

President Biden signed an Executive Order on July 9, 2021, affirming the administration's policy to (i) support legislative reforms that would lower the prices of prescription drugs, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower-cost generic drugs and biosimilars; and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order also directs the U.S. Department of Health and Human Services, or HHS, to provide a report on actions to combat excessive pricing of prescription drugs, continue to clarify and improve the approval framework for generic drugs and identify and address any efforts to impede generic drug competition, enhance the domestic drug supply chain, reduce the price that the Federal government pays for drugs, and address price gouging in the industry; and directs the FDA to work with states and Indian Tribes that propose to develop

section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA's implementing regulations. The FDA released such implementing regulations on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. In response, authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. If implemented, importation of drugs from Canada and the Most Favored Nation, or MFN, Model may materially and adversely affect the price we receive for any of our commercially approved products. Further, on November 20, 2020, CMS issued an Interim Final Rule implementing the MFN Model under which Medicare Part B reimbursement rates will be calculated for certain drugs based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and would have applied to all U.S. states and territories for a seven-year period beginning January 1, 2021, and ending December 31, 2027. However, on December 29, 2021, CMS rescinded the proposed MFN rule. Additionally, on December 2, 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors have been delayed until January 1, 2023, requiring manufacturers to ensure the full value of co-pay assistance is passed on to the patient or these dollars will count toward the Average Manufacturer Price and Best Price calculation of the drug. On May 21, 2021, PhRMA sued the HHS in the U.S. District Court for the District of Columbia, to stop the implementation of the rule claiming that the rule contradicts federal law surrounding Medicaid rebates. It is unclear how the outcome of this litigation will affect the rule. We cannot predict how the implementation of and any further changes to this rule will affect our business. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the current U.S. presidential administration may reverse or otherwise change these measures, both the current U.S. presidential administration and Congress have indicated that they will continue to seek new legislative measures to control drug costs.

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 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 December 31, 2021 due to 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.

Further, there have been several changes to the 340B Drug Pricing Program, which imposes ceilings on prices that drug manufacturers can charge for medications sold to certain healthcare facilities. On December 27, 2018, the District Court for the District of Columbia invalidated a reimbursement formula change under the 340B Drug Pricing Program, and CMS subsequently altered the fiscal years 2019 and 2018 reimbursement formula on specified covered outpatient drugs. The court ruled this change was not an "adjustment" which was within the Secretary's discretion to make but was instead a fundamental change in the reimbursement calculation. However, most recently, on July 31, 2020, the U.S. Court of Appeals for the District of Columbia Circuit overturned the district court's decision and found that the changes were within the Secretary's authority. On September 14, 2020, the plaintiffs-appellees filed a Petition for Rehearing En Banc (i.e., before the full court), and the court denied this petition on October 16, 2020. Plaintiffs-appellees filed a petition for a writ of certiorari at the Supreme Court on February 10, 2021. On Friday July 2, 2021, the Supreme Court granted the petition. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any.

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 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. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for the purpose of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how other healthcare reform measures of the Biden administration or other efforts, if any, to challenge, repeal or replace the ACA will impact our business.

At the state level, legislatures have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical 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 healthcare 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 healthcare 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 Control, 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.

We remain focused on these laws and the activities they regulate and, as detailed above, maintain a global compliance program designed to empower our business to operate in compliance with their requirements.

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 or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal FCA or federal civil money penalties.
- 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 civil monetary penalties laws, which impose civil fines for, among other things, the offering or transfer of remuneration to a Medicare or state healthcare program beneficiary if the person knows or should know it is likely to influence the beneficiary's selection of a particular provider, practitioner, or supplier of services reimbursable by Medicare or a state healthcare program, unless an exception applies.
- 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.
- Federal "sunshine" requirements imposed by the ACA on drug, device, biological and medical supply manufacturers when payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to HHS under the Open Payments Program, information regarding any payment or other "transfer of value" made or distributed to physicians (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. Failure to submit required information may result in civil monetary penalties for all payments, transfers of value or ownership or investment interests that are not timely, accurately, and completely reported in an annual submission. Effective January 1, 2022, these reporting obligations extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners.
- Federal price reporting laws, which require manufacturers to calculate and report complex pricing metrics to government programs, where such reported prices may be used in the calculation of reimbursement and/or discounts on approved products.
- Federal statutory and regulatory requirements applicable to pricing and sales of product to Federal Government Agencies.
- Federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

- State and foreign laws comparable to each of the above federal laws, including in the EU laws prohibiting giving healthcare professionals any gift or benefit in kind as an inducement to prescribe our products, national transparency laws requiring the public disclosure of payments made to healthcare professionals and institutions, and data privacy laws, in addition to anti-kickback and false claims laws applicable to commercial insurers and other non-federal payors, requirements for mandatory corporate regulatory compliance programs, and laws relating to government reimbursement programs, patient data privacy and security.
- European Privacy Laws including Regulation 2016/679, known as the General Data Protection Regulation, or the GDPR, and the e-Privacy Directive (202/58/EC), and the national laws implementing each of them, as well as the privacy laws of Japan and other territories. Failure to comply with our obligations under the privacy regime could expose us to significant fines and/or adverse publicity, which could have material adverse effects on our reputation and business.
- The California Consumer Privacy Act of 2018, or CCPA, effective as of January 1, 2020, that gives California residents expanded rights to access and require deletion of their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation.

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

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 Office of Inspector General of the Department of Health and Human Services, any of which could adversely affect our financial results. As detailed above, we remain focused on enhancing 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 and UK. 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.

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 and UK, 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.

Significantly, 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. In the past, companies in the U.S. were able to rely upon the EU-U.S. and the Swiss-U.S. Privacy Shield frameworks to legitimize data transfers from the EU and the UK to the U.S. In July 2020, the Court of Justice of the European Union, or CJEU, in Case C-311/18 (Data Protection Commissioner v Facebook Ireland and Maximillian Schrems, or Schrems II) invalidated the EU-U.S. Privacy Shield on the grounds that the Privacy Shield failed to offer adequate protections to EU personal data transferred to the U.S. The CJEU, in the same decision, deemed that the Standard Contractual Clauses, or SCCs, published by the EC are valid. However, the CJEU ruled that transfers made pursuant to the SCCs need to be assessed on a case-by-case basis to ensure the law in the recipient country provides "essentially equivalent" protections to safeguard the transferred personal data as the EU, and required businesses to adopt supplementary measures if such standard is not met. Subsequent guidance published by the European Data Protection Board in June 2021 described what such supplementary measures must be, and stated that businesses should avoid or cease transfers of personal data if, in the absence of supplementary measures, equivalent protections cannot be afforded. On June 4, 2021, the EC published new versions of the SCCs, which seek to address the issues identified by the CJEU's Schrems II decision and provide further details regarding the transfer assessments that the parties are required to conduct when implementing the New SCCs. However, there continue to be concerns about whether the SCCs and other mechanisms will face additional challenges. Similarly, the Swiss data protection authority determined the Swiss-U.S. Privacy Shield framework was no longer a valid mechanism for Swiss-U.S. data transfers and also raised questions about the validity of the SCCs as a mechanism for transferring personal data from Switzerland. While Standard Contractual Clauses provide an alternative to our Privacy Shield certification for EU-U.S. data flows, the decision (and certain regulatory guidance issued in its wake) casts doubt on the legality of EU-U.S. data flows in general. Any inability to transfer personal data from the EU to the U.S. in compliance with data protection laws may impede our ability to conduct trials and may adversely affect our business and financial position. The UK is not subject to the EC's new SCCs but has published a draft version of its International Transfer Agreement, which, once finalized, will enable transfer from the UK.

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 or UK (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 and/or UK 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.

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

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

Under the Budget Control Act of 2011, the failure of Congress to enact deficit reduction measures of at least $1.2 trillion for the years 2013 through 2021 triggered automatic cuts to most federal programs. These cuts included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. Certain of these automatic cuts have been implemented resulting in reductions in Medicare payments to physicians, hospitals, and other healthcare providers, among other things. Due to legislation amending the statute, including the Bipartisan Budget Act of 2018, these reductions will stay in effect through 2030 unless additional Congressional action is taken. Pursuant to the CARES Act, as well as subsequent legislation, these reductions have been suspended from May 1, 2020 through December 31, 2021 due to the COVID-19 pandemic. 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. As detailed above, we maintain a global compliance program and remain focused on its evolution and enhancement. Our program includes efforts such as risk assessment and monitoring, fostering a culture encouraging employees and third parties to raise good faith questions or concerns, and defined processes and systems for reviewing and remediating allegations and identified potential concerns. It is not always possible, however, 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 America Invents Act, or 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 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. An oral hearing was held at the EPO on February 17, 2021, where the patent was revoked. A notice of appeal of the EPO's decision was filed on June 23, 2021. 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 products marketed by us or our licensees, our late-stage therapeutic candidates being developed by us or our licensees, including vutrisiran, zilebesiran 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 vutrisiran, 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 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 and the related Exclusive TTR License and AT3 License Terms. Ionis claimed it was owed technology access fees, or TAFs, based on rights granted and amounts paid to us in connection with the Sanofi restructuring. Ionis later filed a Demand for Arbitration with the Boston office of the American Arbitration Association against us, asserting, among other things, breach of contract. Upon completion of the arbitration process in the second quarter of 2020, in October 2020, a partial award was issued by the arbitration panel that sought 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.

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, CMOs, 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 BridgeBio Pharma, Inc. (formerly Eidos Therapeutics, Inc.), or BridgeBio, announced topline results from Part A of its Phase 3 clinical trial of acoramidis, a TTR stabilizer, in ATTR-CM in December 2021, which did not meet the primary endpoint of the study at month 12. BridgeBio initiated enrollment in Part B of its Phase 3 clinical trial of acoramidis in ATTR-PN patients in the fourth quarter of 2020, and anticipates topline results in 2023. While we believe that ONPATTRO has and will continue to have a competitive product profile for the treatment of patients with hATTR amyloidosis with polyneuropathy, and if approved, that vutrisiran will have a competitive product profile in this indication, 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 or negative data and/or the commercial success or failure of competitive products could negatively impact our stock price. For example, our stock price was negatively impacted by the results of Part A of BridgeBio's Phase 3 clinical trial.

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 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 primary hyperoxaluria. In July 2019, the FDA granted a Breakthrough Therapy Designation to nedosiran for the treatment of patients with primary hyperoxaluria, and in August 2021, Dicerna (acquired by Novo Nordisk in December 2021) announced positive topline results in its PHYOX2 pivotal

clinical trial of nedosiran and expects to submit an NDA to the FDA in the first quarter of 2022. 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, 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, 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 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. 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 (and transferred to the United States District Court for the District of Massachusetts by stipulation of the parties and Order of the Court dated November 20, 2018). The complaint, as amended, or the Complaint, alleged 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 sought 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 to dismiss and dismissed the Complaint without prejudice, and subsequently in March 2021 denied plaintiffs' motion seeking leave to file a further amended complaint. Plaintiffs did not file a notice of appeal from such denial. 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. While we believe the allegations in the New York State Securities Litigation are without merit, in August 2021 the parties reached an agreement in principle to resolve the matter. A hearing is scheduled for April 12, 2022 in the Supreme Court of the State of New York regarding final approval of the settlement. Proceedings in the First Department are adjourned until February 2022, subject to further adjournment, pending final approval of any settlement. 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. In addition, we have obligations to indemnify third parties in connection with certain litigation, including the New York State matter, and such obligations are not covered by insurance.

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 January 31, 2022, 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, 2022 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*	61,000	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	September 2027	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 and 13th 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 the Lease. On September 30, 2020, we entered into a First Amendment to the 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. 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."

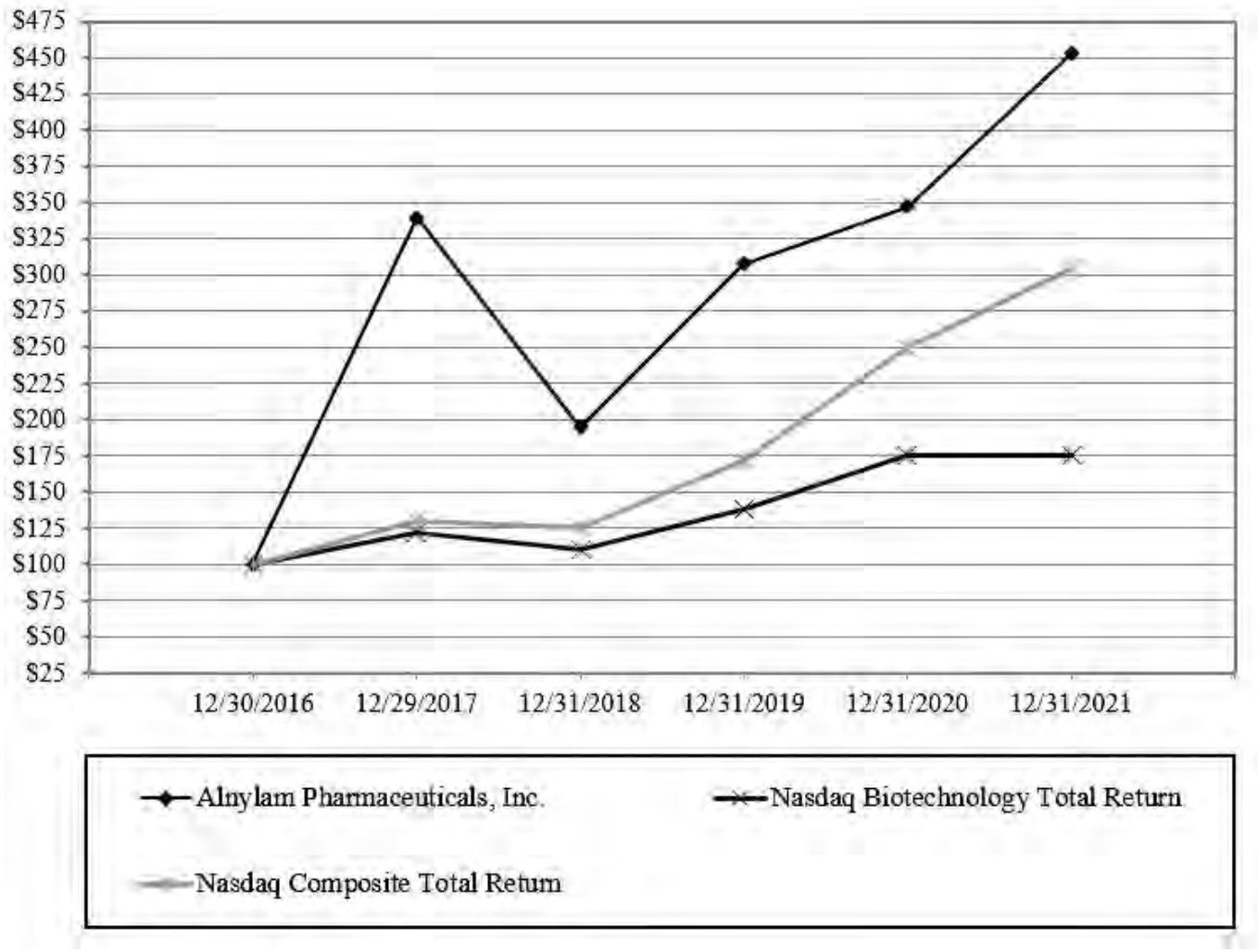
Holders of Record

At January 31, 2022, there were 24 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.

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 2016, to the close of the last trading day of 2021, 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

	12/30/2016	12/29/2017	12/31/2018	12/31/2019	12/31/2020	12/31/2021
Alnylam Pharmaceuticals, Inc.	$ 100.00	$ 339.34	$ 194.74	$ 307.61	$ 347.14	$ 452.94
Nasdaq Composite Total Return	$ 100.00	$ 129.64	$ 125.96	$ 172.17	$ 249.51	$ 304.85
Nasdaq Biotechnology Total Return	$ 100.00	$ 121.63	$ 110.85	$ 138.69	$ 175.33	$ 175.37

ITEM 6. RESERVED

Not applicable.

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 five late-stage investigational programs advancing towards potential commercialization. In Part I, Item 1. "Business" you can also find a summary of key events in 2021 and 2022 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, 2021, we had an accumulated deficit of $5.44 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, as of December 31, 2021, we generate worldwide product revenues from three commercialized products, ONPATTRO, GIVLAARI and OXLUMO, primarily in the U.S., Europe and Japan. 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 and Novartis. In addition to revenues from the commercial sales of our approved products 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. Such alliances include, or may include in the future, 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 the sale of equity or debt.

Results of Operations

The following data summarizes the results of our operations:

	Year Ended December 31,		
(In thousands)	2021	2020	2019
Revenues	$ 844,287	$ 492,853	$ 219,750
Operating costs and expenses	$ 1,552,939	$ 1,321,291	$ 1,159,181
Loss from operations	$ (708,652)	$ (828,438)	$ (939,431)
Net loss	$ (852,824)	$ (858,281)	$ (886,116)

For discussion of our 2020 results and a comparison with 2019 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, 2020 that was filed with the SEC on February 11, 2021.

Discussion of Results of Operations

Revenues

Total revenues consist of the following:

(In thousands, except percentages)	Years Ended December 31, 2021	2020	2019	2021 vs 2020 $ Change	% Change	2020 vs 2019 $ Change	% Change
Net product revenues	$ 662,138	$ 361,520	$ 166,537	$ 300,618	83 %	$ 194,983	117 %
Net revenues from collaborations	180,953	131,333	53,213	49,620	38 %	78,120	147 %
Royalty revenue	1,196	—	—	1,196	N/A	—	N/A
Total	$ 844,287	$ 492,853	$ 219,750	$ 351,434	71 %	$ 273,103	124 %

Net Product Revenues

Net product revenues consist of the following:

(In thousands, except percentages)	Year Ended December 31, 2021	2020	2019	2021 vs 2020 $ Change	% Change	2020 vs 2019 $ Change	% Change
ONPATTRO							
United States	$ 213,210	$ 151,574	$ 116,302	$ 61,636	41 %	$ 35,272	30 %
Europe	190,435	107,755	43,980	82,680	77 %	63,775	145 %
Rest of World (primarily Japan)	71,092	46,752	6,105	24,340	52 %	40,647	666 %
Total	$ 474,737	$ 306,081	$ 166,387	$ 168,656	55 %	$ 139,694	84 %
GIVLAARI							
United States	$ 92,747	$ 42,797	$ 150	$ 49,950	117 %	$ 42,647	28,431 %
Europe	30,895	12,000	—	18,895	157 %	12,000	N/A
Rest of World	4,173	309	—	3,864	1250 %	309	N/A
Total	$ 127,815	$ 55,106	$ 150	$ 72,709	132 %	$ 54,956	36,637 %
OXLUMO							
United States	$ 18,876	$ —	$ —	$ 18,876	N/A	$ —	N/A
Europe	38,949	333	—	38,616	11,596 %	333	N/A
Rest of World	1,761	—	—	1,761	N/A	—	N/A
Total	$ 59,586	$ 333	$ —	$ 59,253	17,794 %	$ 333	N/A
Total net product revenues	$ 662,138	$ 361,520	$ 166,537	$ 300,618	83 %	$ 194,983	117 %

Net product revenues increased during the year ended December 31, 2021, compared to the year ended December 31, 2020, as a result of the continued, global expansion of ONPATTRO and GIVLAARI into additional major markets and increased patients on therapy, in addition to sales generated from our third commercial product, OXLUMO, following regulatory approvals in the fourth quarter of 2020.

We expect net product revenues to increase during 2022, as compared to 2021, as we continue to add new patients onto our commercial products, as well as launch vutrisiran in the U.S. and 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, 2021 and 2020.

Net Revenues from Collaborations and Royalty Revenue

Net revenues from collaborations consist of the following:

	Years Ended December 31,			2021 vs 2020		2020 vs 2019	
(In thousands, except percentages)	2021	2020	2019	$ Change	% Change	$ Change	% Change
Regeneron Pharmaceuticals	$ 113,226	$ 74,072	$ 26,075	$ 39,154	53 %	$ 47,997	184 %
Novartis AG	49,120	22,208	2,315	26,912	121 %	19,893	859 %
Vir Biotechnology	16,897	31,396	12,809	(14,499)	(46)%	18,587	145 %
Other	1,710	3,657	12,014	(1,947)	(53)%	(8,357)	(70)%
Total	$ 180,953	$ 131,333	$ 53,213	$ 49,620	38 %	$ 78,120	147 %

Net revenues from collaborations increased during the year ended December 31, 2021, as compared to the year ended December 31, 2020, primarily due to increased revenue recognized in connection with our collaboration agreements with Regeneron and Novartis, including the achievement of a $25 million regulatory milestone payment for Leqvio associated with FDA approval in Q4 2021. These increases were offset by decreased activities in connection with our collaboration agreement with Vir.

We earn royalty revenue from global net sales of Leqvio by our partner, Novartis. In December 2020, Leqvio received marketing authorization from the EC for the treatment of adults with hypercholesterolemia or mixed dyslipidemia, and in December 2021, Leqvio was approved by the FDA for the treatment of adults with HeFH or ASCVD. During the year ended December 31, 2021, we earned $1.2 million in royalty revenue.

We expect combined net revenues from collaborations and royalty revenue to moderately increase in 2022, as compared to 2021, due to increased reimbursable activities, anticipated achievement of milestones under our collaboration agreements, and increased royalties associated with sales of Leqvio.

Operating Costs and Expenses

Operating costs and expenses consist of the following:

	Year Ended December 31,			2021 vs 2020		2020 vs 2019	
(In thousands, except percentages)	2021	2020	2019	$ Change	% Change	$ Change	% Change
Cost of goods sold	$ 115,005	$ 74,185	$ 25,062	$ 40,820	55 %	$ 49,123	196 %
Cost of collaborations and royalties	25,139	3,867	—	21,272	550 %	3,867	N/A
Research and development	792,156	654,819	655,114	137,337	21 %	(295)	— %
Selling, general and administrative	620,639	588,420	479,005	32,219	5 %	109,415	23 %
Total	$1,552,939	$1,321,291	$1,159,181	$ 231,648	18 %	$ 162,110	14 %

Cost of Goods Sold

Cost of goods sold as a percentage of net product revenues decreased to 17.4% for the year ended December 31, 2021, as compared to 20.5% for the year ended December 31, 2020, primarily due to decreased charges in 2021 as a result of manufacturing facilities operating at near full capacity compared to 2020.

We anticipate variability in our cost of goods sold as a percentage of net product revenues due to the timing of manufacturing runs and utilization and the depletion of zero-cost inventories, as well as future product launches. We expect cost of goods sold will increase during 2022, as compared to 2021, primarily as a result of an expected increase in net product sales as well as the sale of capitalized inventory.

Cost of collaborations and royalties

Cost of collaborations and royalties increased during the year ended December 31, 2021, as compared to the year ended December 31, 2020, primarily due to an increase in GalNAc material supply to Novartis to support its continued, global launch of Leqvio, as well as its ongoing clinical trials.

We expect cost of collaborations and royalties to remain relatively consistent during 2022, as compared to 2021, due to variability of GalNAc material supplied to Novartis to support the manufacturing of Leqvio.

Research and Development

Research and development expenses consist of the following:

(In thousands, except percentages)	Year Ended December 31, 2021	2020	2019	2021 vs 2020 $ Change	% Change	2020 vs 2019 $ Change	% Change
Clinical trial and manufacturing	$ 313,753	$ 218,752	$ 203,897	$ 95,001	43 %	$ 14,855	7 %
Compensation and related	196,134	190,705	157,001	5,429	3 %	33,704	21 %
Facilities-related	81,462	69,769	54,650	11,693	17 %	15,119	28 %
External services	70,679	70,120	75,448	559	1 %	(5,328)	(7)%
Stock-based compensation	68,415	60,464	88,930	7,951	13 %	(28,466)	(32)%
Lab supplies, materials and other	44,881	42,229	38,158	2,652	6 %	4,071	11 %
License fees	16,832	2,780	37,030	14,052	505 %	(34,250)	(92)%
Total	$ 792,156	$ 654,819	$ 655,114	$ 137,337	21 %	$ (295)	— %

Research and development expenses increased during the year ended December 31, 2021, as compared to the year ended December 31, 2020, primarily due to the following:

- Increased clinical trial and manufacturing expenses primarily related to increased expenses associated with activities related to the advancement of our HELIOS B, APOLLO B, KARDIA-1 and KARDIA-2 clinical programs; and
- Increased license fees expense resulting from upfront payments due upon the execution of certain collaboration agreements.

During the years ended December 31, 2021 and 2020, in connection with advancing activities under our collaboration agreements, we incurred research and development expenses, primarily related to external development and clinical expenses, including the manufacture of clinical product.

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

(In thousands)	Year Ended December 31, 2021	2020	2019
Regeneron Pharmaceuticals	$ 73,411	$ 57,833	$ 24,916
Vir Biotechnology	13,349	30,644	15,479
Other	2,226	4,656	16,577
Total	$ 88,986	$ 93,133	$ 56,972

Selling, General and Administrative

Selling, general and administrative expenses consist of the following:

(In thousands, except percentages)	Year Ended December 31, 2021	2020	2019	2021 vs 2020 $ Change	% Change	2020 vs 2019 $ Change	% Change
Compensation and related	$ 224,237	$ 200,071	$ 148,271	$ 24,166	12 %	$ 51,800	35 %
Consulting and professional services	201,841	176,097	155,843	25,744	15 %	20,254	13 %
Stock-based compensation	97,302	79,409	85,911	17,893	23 %	(6,502)	(8)%
Facilities-related	44,768	45,387	35,779	(619)	(1)%	9,608	27 %
Other	52,491	87,456	53,201	(34,965)	(40)%	34,255	64 %
Total	$ 620,639	$ 588,420	$ 479,005	$ 32,219	5 %	$ 109,415	23 %

Selling, general and administrative expenses increased during the year ended December 31, 2021, as compared to the year ended December 31, 2020, primarily due to the following:

- Increased compensation and related expenses and stock-based compensation expense as a result of increased commercial and medical affairs headcount to support our *Alnylam P^{5}x25* strategy; and
- Increased consulting and professional services expenses as a result of increased commercial-related services as well as the continued expansion of our commercial products into additional major markets.

Offset by:

- Decreased other expenses due to a change in an estimate of contingent liabilities related to our arbitration with Ionis in 2020.

We expect that research and development expenses combined with selling, general and administrative expenses will increase during 2022, as compared to 2021, as we continue to advance and develop our platform and pipeline, advance our product candidates, including partnered programs, into later-stage development, prepare regulatory submissions and continue to build-out our global commercial and compliance infrastructure and field team to support ONPATTRO, GIVLAARI, OXLUMO and potentially additional product launches, including vutrisiran. 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.

Other (Expense) Income

Other (expense) income consists of the following:

	Year Ended December 31,			2021 vs 2020		2020 vs 2019	
(In thousands, except percentages)	**2021**	**2020**	**2019**	**$ Change**	**% Change**	**$ Change**	**% Change**
Interest expense	$(143,021)	$ (84,496)	$ —	$ (58,525)	69 %	$ (84,496)	N/A
Interest income	1,579	11,809	33,448	(10,230)	(87)%	(21,639)	(65)%
Other (expense) income, net							
Realized and unrealized gains on marketable equity securities	55,695	54,042	11,288	1,653	3 %	42,754	379 %
Change in fair value of development derivative liability	(38,433)	(17,185)	—	(21,248)	124 %	(17,185)	N/A
Change in fair value of liability obligation	—	—	9,422	—	N/A	(9,422)	(100)%
Other (expense) income	(19,312)	8,668	20	(27,980)	(323)%	8,648	43,240 %
Total	$(143,492)	$ (27,162)	$ 54,178	$(116,330)	428 %	$ (81,340)	(150)%

Total other expense increased during the year ended December 31, 2021, as compared to the year ended December 31, 2020, primarily due to increased interest expense associated with the sale of future royalties and the drawdown of our credit facility beginning in December 2020, increased expense associated with the mark-to-market adjustment related to the development derivative liability and increased other expense as a result of unfavorable foreign currency remeasurement.

Liquidity and Capital Resources

The following table summarizes our cash flow activities:

(In thousands)	Year Ended December 31, 2021	2020	2019
Net loss	$ (852,824)	$ (858,281)	$ (886,116)
Non-cash adjustments to reconcile net loss to net cash used in operating activities:	373,954	256,021	205,308
Changes in operating assets and liabilities:	(162,823)	(12,701)	402,381
Net cash used in operating activities	(641,693)	(614,961)	(278,427)
Net cash used in investing activities	(273,300)	(435,518)	(417,677)
Net cash provided by financing activities	1,247,118	994,979	823,184
Effect of exchange rate changes on cash, cash equivalents and restricted cash	(9,018)	4,918	(83)
Net increase (decrease) in cash, cash equivalents and restricted cash	323,107	(50,582)	126,997
Cash, cash equivalents and restricted cash, beginning of period	499,046	549,628	422,631
Cash, cash equivalents and restricted cash, end of period	$ 822,153	$ 499,046	$ 549,628

Operating Activities

Net cash used in operating activities increased during the year ended December 31, 2021, compared to the year ended December 31, 2020, primarily due to increased cash disbursements related to working capital payments partially offset by stronger cash receipts from increased product sales.

Investing Activities

Net cash used in investing activities decreased during the year ended December 31, 2021, compared to the year ended December 31, 2020, primarily due to decreased purchases, sales and maturities of our marketable securities.

Financing Activities

Net cash provided by financing activities increased during the year ended December 31, 2021, compared to the year ended December 31, 2020, primarily due to proceeds of $500.0 million in connection with drawdown on our credit agreement and increased net proceeds of $45.8 million from the issuance of common stock in connection with stock option exercises and other types of equity, compared to the prior year proceeds of $200.0 million in connection with the first drawdown on our credit facility and net proceeds of $99.5 million from our issuance of common stock to certain affiliates of The Blackstone Group Inc.

Additional Capital Requirements

We currently have programs focused on a number of therapeutic areas and, as of December 31, 2021, have received regulatory approval and commercially launched three products: ONPATTRO, GIVLAARI and OXLUMO. In early 2021, we announced *Alnylam P^{5}x25,* which is aimed at our planned transition to a top five biotech. 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, including vutrisiran, or successfully expand the indication for our approved products, including ONPATTRO (and vutrisiran, if approved), 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, commercial and compliance 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, 2021, together with the cash we expect to generate from product sales and under our current alliances, including milestones and royalties on Leqvio sales, 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. Recent and expected working and other capital requirements, in addition to the above matters, also include the items described below:

- Amounts related to future lease payments for operating lease obligations at December 31, 2021 totaled $503.6 million, with$41.8 million expected to be paid within the next 12 months.
- Our cash operating expenditures were $641.7 million in 2021 and $615.0 million in 2020, and we expect to increase our investment in operations in 2022.

- Cash outflows for capital expenditures were $76.4 million in 2021 and $70.4 million in 2020. We expect capital expenditures to increase in 2022 to support the increase in our manufacturing and production capacity needs.
- Amounts related to future long-term debt total $675.7 million, of which we do not expect to make payments on principal within the next 12 months.
- Payments associated with the liability related to the sale of future royalties were approximately $0.4 million in 2021, with $37.1 million to be paid within the next 12 months.

Since we commenced operations in 2002, we have generated significant losses and as of December 31, 2021, we had an accumulated deficit of $5.44 billion. As of December 31, 2021, we had cash, cash equivalents and marketable securities of $2.44 billion, compared to $1.87 billion as of December 31, 2020.

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, including vutrisiran.

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 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 estimates for our product revenue allowances and accruals are most significantly affected by chargebacks, which are 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, and rebates that represent 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 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 revenues. We use the expected value method to estimate variable consideration for chargebacks, certain rebates, and other incentives and we use the most likely amount method for certain rebates and trade discounts and allowances.

A 10% increase or decrease in these estimates impacts net sales by a corresponding increase or decrease of approximately $5.0 million.

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.

For elements of collaboration arrangements that are accounted for pursuant to ASC Topic 606, Revenue from Contracts with Customers, or 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. 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, for example based on actual costs incurred relative to total forecasted costs to be incurred over the period the transfer of goods or services occurs. 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. Revenue to be recognized is equal to the total transaction price multiplied by the ratio of actual expense incurred divided by total forecasted expense.

A 10% increase or decrease in the transaction price impacts net revenues from collaborators by a corresponding increase or decrease of approximately $26.0 million. A 10% increase or decrease in the total forecasted costs to be incurred over the period the transfer of goods or services occurs impacts net revenues from collaborators by a corresponding decrease or increase of approximately $24.0 million.

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 Leqvio's global net revenue. Third-party forecasts are updated periodically as new data is obtained with regards to Leqvio's global launch progress or as sales information becomes available. Increases, decreases or a shift in timing of estimated revenues affects the interest rate utilized in the calculation of the liability related to the sale of future royalties. An increase or decrease of 5% to the interest rate would result in an increase or decrease to our liability related to the sale of future royalties of approximately $14.5 million.

Development Derivative Liability

In August 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 zilebesiran, two of our cardiometabolic programs. As consideration for Blackstone Life Sciences' funding for certain vutrisiran and zilebesiran clinical development costs, we have agreed to pay Blackstone Life Sciences fixed success-based payments upon achievement of specific milestones for vutrisiran and zilebesiran as well as a 1% royalty on net sales of vutrisiran for ten years.

The development derivative liability is recorded at fair value and represents our current estimate of the expected future payments to Blackstone Life Sciences. The development derivative liability is based on the probability weighted present value of the estimated cash flows pursuant to contractual terms of the Funding Agreement. The most significant assumptions in determining the development derivative liability are the probability of success for the clinical development and regulatory approval of vutrisiran and zilebesiran and our current cost of borrowing. Estimates of the probability of success and our cost of borrowing are based on what we believe to be reasonable and supportable assumptions and require management's judgment. Actual results could vary materially from these estimates.

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, 2021 and 2020, a hypothetical increase in interest rates of 50 basis points across the entire yield curve on our holdings would have resulted in an immaterial decrease to the fair value of our holdings.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

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

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Alnylam Pharmaceuticals, Inc. and its subsidiaries (the "Company") as of December 31, 2021 and 2020, 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, 2021, 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, 2021, 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, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021 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, 2021, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

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 Leqvio. The Company recorded a liability related to the sale of future royalties of $1.19 billion as of December 31, 2021 and recognized interest expense on the liability related to the sale of future royalties of $116.9 million for the year ended December 31, 2021.

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 Leqvio.

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 Leqvio. Evaluating management's assumption related to the selection of third-party data used to estimate global net sales of Leqvio involved evaluating whether the assumptions used by management were reasonable considering consistency with industry data.

/s/PricewaterhouseCoopers LLP
Boston, Massachusetts
February 10, 2022

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

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

	December 31, 2021	December 31, 2020
ASSETS		
Current assets:		
Cash and cash equivalents	$ 819,975	$ 496,580
Marketable debt securities	1,548,617	1,333,182
Marketable equity securities	66,972	44,633
Accounts receivable, net	198,571	102,413
Inventory	86,363	75,202
Prepaid expenses and other current assets	88,078	62,767
Receivable related to the sale of future royalties	—	500,000
Total current assets	2,808,576	2,614,777
Property, plant and equipment, net	501,958	465,029
Operating lease right-of-use assets	231,675	241,485
Restricted investments	40,891	40,725
Other assets	60,204	45,045
Total assets	$ 3,643,304	$ 3,407,061
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 73,426	$ 51,966
Accrued expenses	395,174	355,909
Operating lease liability	40,548	36,872
Deferred revenue	149,483	127,207
Liability related to the sale of future royalties	37,079	13,316
Total current liabilities	695,710	585,270
Operating lease liability, net of current portion	281,347	293,039
Deferred revenue, net of current portion	152,360	225,094
Long-term debt, net	675,697	191,278
Liability related to the sale of future royalties, net of current portion	1,151,024	1,058,225
Other liabilities	98,963	37,908
Total liabilities	3,055,101	2,390,814
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, 2021 and December 31, 2020	—	—
Common stock, $0.01 par value per share, 250,000 shares authorized as of December 31, 2021 and December 31, 2020, respectively; 120,182 shares issued and outstanding as of December 31, 2021; 116,427 shares issued and outstanding as of December 31, 2020	1,202	1,164
Additional paid-in capital	6,058,453	5,644,074
Accumulated other comprehensive loss	(33,259)	(43,622)
Accumulated deficit	(5,438,193)	(4,585,369)
Total stockholders' equity	588,203	1,016,247
Total liabilities and stockholders' equity	$ 3,643,304	$ 3,407,061

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,		
	2021	2020	2019
Statements of Operations			
Revenues:			
Net product revenues	$ 662,138	$ 361,520	$ 166,537
Net revenues from collaborations	180,953	131,333	53,213
Royalty revenue	1,196	—	—
Total revenues	844,287	492,853	219,750
Operating costs and expenses:			
Cost of goods sold	115,005	74,185	25,062
Cost of collaborations and royalties	25,139	3,867	—
Research and development	792,156	654,819	655,114
Selling, general and administrative	620,639	588,420	479,005
Total operating costs and expenses	1,552,939	1,321,291	1,159,181
Loss from operations	(708,652)	(828,438)	(939,431)
Other (expense) income:			
Interest expense	(143,021)	(84,496)	—
Interest income	1,579	11,809	33,448
Other (expense) income, net	(2,050)	45,525	20,730
Total other (expense) income, net	(143,492)	(27,162)	54,178
Loss before income taxes	(852,144)	(855,600)	(885,253)
Benefit (provision) for income taxes	(680)	(2,681)	(863)
Net loss	$ (852,824)	$ (858,281)	$ (886,116)
Net loss per common share — basic and diluted	$ (7.20)	$ (7.46)	$ (8.11)
Weighted-average common shares used to compute basic and diluted net loss per common share	118,451	114,986	109,264
Statements of Comprehensive Loss			
Net loss	$ (852,824)	$ (858,281)	$ (886,116)
Other comprehensive income (loss):			
Unrealized (loss) gain on marketable securities	(1,978)	211	558
Foreign currency translation gain (loss)	11,398	(7,081)	(343)
Defined benefit pension plans, net of tax	943	(234)	(3,520)
Total other comprehensive income (loss)	10,363	(7,104)	(3,305)
Comprehensive loss	$ (842,461)	$ (865,385)	$ (889,421)

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, 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	—	—	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	—	—	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
Exercise of common stock options, net of tax withholdings	2,978	30	232,456	—	—	232,486
Issuance of common stock under equity plans	777	8	13,623	—	—	13,631
Stock-based compensation expense	—	—	168,300	—	—	168,300
Other comprehensive gain	—	—	—	10,363	—	10,363
Net loss	—	—	—	—	(852,824)	(852,824)
Balance as of December 31, 2021	120,182	$ 1,202	$ 6,058,453	$ (33,259)	$ (5,438,193)	$ 588,203

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,		
	2021	**2020**	**2019**
Cash flows from operating activities:			
Net loss	$ (852,824)	$ (858,281)	$ (886,116)
Non-cash adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	47,567	34,772	17,175
Amortization and interest accretion related to operating leases	42,127	39,663	37,193
Non-cash interest expense on liability related to the sale of future royalties	116,562	84,496	—
Stock-based compensation	165,717	139,873	174,841
Realized and unrealized gain on marketable equity securities	(55,695)	(54,042)	(11,288)
Other	57,676	11,259	(12,613)
Changes in operating assets and liabilities:			
Accounts receivable, net	(101,799)	(56,236)	(24,238)
Inventory	(26,415)	(35,426)	(32,411)
Prepaid expenses and other assets	(32,093)	13,017	(9,530)
Accounts payable, accrued expenses and other liabilities	88,240	143,732	92,354
Deferred revenue	(50,404)	(43,965)	392,251
Operating lease liability	(40,352)	(33,823)	(16,045)
Net cash used in operating activities	(641,693)	(614,961)	(278,427)
Cash flows from investing activities:			
Purchases of property, plant and equipment	(76,372)	(70,361)	(140,156)
Purchases of marketable securities	(1,656,114)	(2,025,626)	(2,075,925)
Sales and maturities of marketable securities	1,463,550	1,691,669	1,775,404
Proceeds from maturity of restricted investments	41,975	—	30,000
Purchases of restricted investments	(42,141)	(25,900)	—
Other investing activities	(4,198)	(5,300)	(7,000)
Net cash used in investing activities	(273,300)	(435,518)	(417,677)
Cash flows from financing activities:			
Proceeds from exercise of stock options and other types of equity, net	246,268	200,484	71,284
Proceeds from the sale of future royalties	500,000	500,000	—
Proceeds from development derivative	19,600	8,400	—
Offering proceeds, net of costs	—	—	381,900
Proceeds from term loan facility	500,000	200,000	—
Proceeds from issuance of common stock to strategic partners, net of closing costs	—	99,498	400,000
Other financing activities	(18,750)	(13,403)	(30,000)
Net cash provided by financing activities	1,247,118	994,979	823,184
Effect of exchange rate changes on cash, cash equivalents and restricted cash	(9,018)	4,918	(83)
Net increase (decrease) in cash, cash equivalents and restricted cash	323,107	(50,582)	126,997
Cash, cash equivalents and restricted cash, beginning of period	499,046	549,628	422,631
Cash, cash equivalents and restricted cash, end of period	$ 822,153	$ 499,046	$ 549,628
Supplemental disclosure of cash flows:			
Cash paid for interest	$ 24,657	$ —	$ 172
Supplemental disclosure of noncash investing and financing activities:			
Capital expenditures included in accounts payable and accrued expenses	$ 13,599	$ 14,518	$ 14,876
Lease liabilities arising from obtaining right-of-use assets	$ 7,932	$ 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 ribonucleic acid interference, or RNAi. We are committed to the advancement of our company strategy of building a multi-product, global, commercial biopharmaceutical company with a deep and sustainable clinical pipeline of RNAi therapeutics for future growth and a robust, organic research engine for sustainable innovation and great potential for patient impact. Since inception, we have focused on discovering, developing and commercializing RNAi therapeutics by establishing and maintaining a strong intellectual property position in the RNAi field, establishing strategic alliances with leading pharmaceutical and life sciences companies, generating revenues through licensing agreements, and ultimately developing and commercializing RNAi therapeutics globally, either independently or with our strategic partners. We have devoted substantially all of our efforts to business planning, research, development, manufacturing and early commercial efforts, acquiring, filing and expanding intellectual property rights, recruiting management and technical staff, and raising capital.

In early 2021, we launched our *Alnylam P^{5}x25* strategy, which focuses on our planned transition to a top five biotech company by the end of 2025. With *Alnylam P^{5}x25*, 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.

As of December 31, 2021, we have four products that have received marketing approval, including one partnered product, and five late-stage investigational programs advancing towards potential commercialization. We currently generate worldwide product revenues from three commercialized products, ONPATTRO, GIVLAARI and OXLUMO, primarily in the United States, or U.S., Europe and Japan.

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 ongoing 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.

Liquidity

Based on our current operating plan, we believe that our cash, cash equivalents and marketable securities as of December 31, 2021, together with the cash we expect to generate from product sales and under our current alliances, including milestones and royalties on Leqvio sales, will be sufficient to enable us to advance our *Alnylam P^{5}x25* strategy for at least the next 12 months from the filing of this Annual Report on Form 10-K.

Concentrations of Credit Risk and Significant Customers

Financial instruments that potentially expose us to concentrations of credit risk primarily consist of cash, cash equivalents and marketable securities. As of December 31, 2021 and 2020, 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, 2021, 2020 and 2019, our revenues were generated primarily from product sales to distributors and collaborations with strategic partners. For the years ended December 31, 2021, 2020 and 2019, 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,		
	2021	2020	2019
Distributor A	27 %	31 %	44 %
Regeneron Pharmaceuticals	11 %	12 %	*

* 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,	
	2021	2020
Novartis AG	20 %	16 %
Distributor A	14 %	19 %
Regeneron Pharmaceuticals	12 %	11 %
Distributor B	10 %	14 %

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, 2021, 2020 or 2019. 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, 2021 and 2020, 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. 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, 2021, 2020 and 2019, we recorded $36.8 million, $30.2 million and $16.6 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

We determine if an arrangement is a lease at contract inception based on the facts and circumstances present in the arrangement. All of our leases are classified as operating leases. 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, 2021 and 2020, 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.

Cost of Collaborations and Royalties

Cost of collaborations and royalties includes costs we incur in connection with providing commercial drug supplies, such as GalNAc material, to collaborators, in addition to royalties we owe to third parties on the net sales of licensed products by Novartis.

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, 2021, 2020 or 2019.

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, 2021, 2020 and 2019, we charged to research and development expense costs associated with license fees of $16.8 million, $2.8 million and $37.0 million, respectively.

Stock-Based Compensation

We recognize stock-based compensation expense for grants under our stock incentive plans and employee stock purchase plan. We account for all stock-based awards granted to employees at their fair value and recognize compensation expense over the vesting period of the award. Determining the amount of stock-based compensation to be recorded requires us to develop estimates of fair values of stock options as of the grant date. We calculate the grant date fair values of stock options using the Black-Scholes valuation model, which requires the input of subjective assumptions, including but not limited to expected stock price volatility over the term of the awards and the expected term of stock options. The fair value of restricted stock awards granted to employees is based upon the quoted closing market price per share on the date of grant.

We have performance conditions included in certain of our restricted stock awards that are based upon the achievement of pre-specified clinical development, regulatory, commercial and/or financial performance 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 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 Leqvio'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)	**2021**	**2020**	**2019**
Options to purchase common stock	10,015	11,692	13,069
Unvested restricted common stock	1,210	1,160	749
Total	11,225	12,852	13,818

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, 2021 and 2020, substantially all of our consolidated property, plant and equipment, net was from U.S. operations. For the years ended December 31, 2021, 2020 and 2019, 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 December 2019, the Financial Accounting Standards Board, or FASB, issued ASU 2019-12, Income Taxes (Topic 740): Simplifying the Accounting for Taxes, 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.

3. NET PRODUCT REVENUES

Net product revenues consist of the following:

(In thousands)	Year Ended December 31, 2021	2020	2019
ONPATTRO			
United States	$ 213,210	$ 151,574	$ 116,302
Europe	190,435	107,755	43,980
Rest of World (primarily Japan)	71,092	46,752	6,105
Total	$ 474,737	$ 306,081	$ 166,387
GIVLAARI			
United States	$ 92,747	$ 42,797	$ 150
Europe	30,895	12,000	—
Rest of World	4,173	309	—
Total	$ 127,815	$ 55,106	$ 150
OXLUMO			
United States	$ 18,876	$ —	$ —
Europe	38,949	333	—
Rest of World	1,761	—	—
Total	$ 59,586	$ 333	$ —
Total net product revenues	$ 662,138	$ 361,520	$ 166,537

As of December 31, 2021 and 2020, net product revenue-related receivables of $124.9 million and $68.9 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, 2021			
(In thousands)	Chargebacks and Rebates	Trade Discounts and Allowances	Returns Reserve and Other Incentives	Total
Beginning balance	$ 90,705	$ 639	$ 3,763	$ 95,107
Provision related to current period sales	167,691	8,064	12,223	187,978
Credit or payments made during the period for current year sales	(75,073)	(7,665)	(5,190)	(87,928)
Credit or payments made during the period for prior year sales	(62,641)	(516)	(684)	(63,841)
Total	$ 120,682	$ 522	$ 10,112	$ 131,316

	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 period sales	(2,995)	(33)	(1,213)	(4,241)
Total	$ 90,705	$ 639	$ 3,763	$ 95,107

During the year ended December 31, 2021, we paid $56.4 million attributed to the finalization of pricing and reimbursement for the sale of ONPATTRO in France.

4. NET REVENUES FROM COLLABORATIONS

Net revenues from collaborations consist of the following:

	Year Ended December 31,		
(In thousands)	2021	2020	2019
Regeneron Pharmaceuticals	$ 113,226	$ 74,072	$ 26,075
Novartis AG	49,120	22,208	2,315
Vir Biotechnology	16,897	31,396	12,809
Other	1,710	3,657	12,014
Total	$ 180,953	$ 131,333	$ 53,213

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

	As of December 31,	
(In thousands)	2021	2020
Receivables included in "Accounts receivable, net"	$ 73,266	$ 33,542
Contract liabilities included in "Deferred revenue"	$ 88,627	$ 120,021

We recognized revenue of $62.9 million and $54.4 million in the years ended December 31, 2021 and 2020, 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 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,								
	2021			2020			2019		
(In thousands)	Clinical Trial and Manufacturing	External Services	Other	Clinical Trial and Manufacturing	External Services	Other	Clinical Trial and Manufacturing	External Services	Other
Regeneron	$ 24,989	$ 840	$ 47,582	$ 13,302	$ 171	$ 44,360	$ 2,793	$ 344	$ 21,779
Vir	9,546	723	3,080	18,470	584	11,590	10,353	381	4,745
Other	765	52	1,409	1,643	181	2,832	13,530	334	2,713
Total	$ 35,300	$ 1,615	$ 52,071	$ 33,415	$ 936	$ 58,782	$ 26,676	$ 1,059	$ 29,237

The research and development expenses incurred for each agreement listed in the table above consist of costs incurred for (i) clinical expenses, including manufacturing of clinical product, (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, 2021, 2020 and 2019, we did not incur material selling, general and administrative expenses related to our collaboration agreements.

In addition, we recognized a reduction to our research and development expenses of $17.1 million, $11.1 million, and $1.1 million for the years ended December 31, 2021, 2020 and 2019, respectively, from cost reimbursement due under certain of our collaboration agreements accounted for under ASC 808.

Product Alliances

Regeneron Pharmaceuticals, Inc.

In April 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. 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 3 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 five 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 covered by the Regeneron Collaboration, with the lead party retaining global development and commercial responsibility. For such 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. 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, 2021, the total transaction price was determined to be $538.4 million, an increase of $6.6 million from December 31, 2020. As of December 31, 2021, 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:

Performance Obligations	Transaction Price Allocated	Deferred Revenue		Accounting Guidance
	As of December 31, 2021	As of December 31, 2021	As of December 31, 2020	
Research Services Obligation	$ 200,680	$ 42,300	$ 54,900	ASC 606
C5 License Obligation	91,700	26,900	58,700	ASC 606
C5 Co-Co Obligation	246,000	212,500	231,400	ASC 808
Total	$ 538,380	$ 281,700	$ 345,000	

Performance Obligations	Revenue Recognized During			Accounting Guidance
	Year Ended December 31, 2021	Year Ended December 31, 2020	Year Ended December 31, 2019	
Research Services Obligation	$ 37,600	$ 44,800	$ 21,000	ASC 606
C5 License Obligation	44,600	7,100	—	ASC 606
C5 Co-Co Obligation	18,900	11,700	2,900	ASC 808
	$ 101,100	$ 63,600	$ 23,900	

As of December 31, 2021, the aggregate amount of the transaction price allocated to the remaining Research Services Obligation and C5 License Obligation that was unsatisfied was $137.3 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.

Novartis AG

2013 Collaboration with The Medicines Company

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, 2021, we have earned $70.0 million of milestones and upon achievement of certain events, we will be entitled to receive additional milestones, up to an aggregate of $110.0 million, including $100.0 million in specified commercialization milestones and $10.0 million in other specified regulatory milestones. In addition, we are 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.

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 core technology patents covering licensed products under the MDCO License Agreement will expire in most countries by 2029. 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, Japan and elsewhere between 2027 and 2036. Certain of 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 (for Alnylam) and any siRNA product (for Novartis) 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 orders will be treated as separate agreements and any associated revenue will be recognized upon transfer of control.

Novartis License Agreement

In December 2021, we and Novartis entered into a collaboration and license agreement, or the Novartis License Agreement, pursuant to which we granted to Novartis an exclusive, worldwide license to develop, manufacture and commercialize siRNAs targeting end-stage liver disease, or ESLD, potentially leading to the development of a treatment designed to promote the regrowth of functional liver cells and to provide an alternative to transplantation for patients with liver failure.

Pursuant to the Novartis License Agreement, we will receive an upfront fee of $12.5 million. 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. 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 under the Novartis License Agreement.

Under the Novartis License Agreement, we will develop and test potential siRNAs using target-specific assays developed by Novartis pursuant to an agreed upon research plan for a specified period referred to as the Collaboration Term. Novartis will reimburse us for the cost of our activities under the research plan, referred to as the DC Workplan, subject to an agreed upon cap. Once a lead candidate is identified, further development and clinical research will be conducted by Novartis. The collaboration is governed by a joint steering committee comprised of an equal number of representatives from each party.

Unless terminated earlier in accordance with the terms of the Novartis License Agreement, the Collaboration Term expires at the earlier of (1) 180 days after completion of the development activities assigned to us as agreed upon between the parties, or (2) December 17, 2024.

Either party may terminate the Novartis 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 three months' prior written notice.

During the term of the Novartis 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 a liver target identified by Novartis, other than a licensed product, without the prior written agreement of the other party, subject to the terms of the Novartis License Agreement.

We identified one performance obligation under the Novartis License Agreement comprised of: i) the exclusive license to develop, manufacture and commercialize siRNAs targeting ESLD; and ii) the obligation to perform work under the DC Workplan. The license is not distinct from the services, including the obligation to deliver development candidates, as Novartis cannot benefit on its own from the value of the license without receipt of such services. 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, 2021, the total transaction price was determined to be approximately $17.0 million, comprised of the $12.5 million upfront payment and estimated variable consideration attributed to work to be performed under the DC Workplan. 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, 2021, no revenue was recognized under the Novartis License Agreement and the aggregate amount of the transaction price allocated to the performance obligation that was unsatisfied was $17.0 million, which is expected to be recognized through the term of the DC Workplan as the services are performed.

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 4 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 would be 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, were responsible for all pre-clinical development costs incurred under such plan for such COVID-19 related activities. In July 2021, we notified Vir that we elected to discontinue ALN-COV, in development for the treatment of COVID-19, and all other COVID-19 research and development activities, based on a portfolio prioritization decision in view of the availability of highly effective vaccines and alternative treatment options, in accordance with our rights under the letter agreement with Vir. Following such discontinuation of COVID-19 related activities, we have no further obligations to work on the COVID-related targets and Vir will have no further rights to such targets under the Vir Agreement.

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

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

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 (through July 2021). 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, 2021, the total transaction price was determined to be $111.0 million, 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, 2021, the aggregate amount of the transaction price allocated to the performance obligation that was unsatisfied was $36.5 million, which is expected to be recognized through the term of the Vir Agreement as the services are performed.

Other Strategic License Agreements

PeptiDream, Inc.

In July 2021, we entered into a license and collaboration agreement with PeptiDream, Inc., or PeptiDream, to discover and develop peptide-siRNA conjugates to create multiple opportunities to deliver RNAi therapeutics to tissues outside the liver. Through this collaboration, the companies will collaborate to select and optimize peptides for targeted delivery of small siRNA molecules to a wide range of cell types and tissues via specific interactions with receptors expressed on the target cells. Under the terms of the agreement, PeptiDream received an upfront payment from us of $10.0 million and we will provide research and development funding over the term of the research collaboration, according to the terms of the PeptiDream agreement. Due to the early stage of these assets, we recorded research and development expense for the upfront payment of $10.0 million during the third quarter of 2021. PeptiDream may also receive payments based on the achievement of specified development, regulatory, and commercial milestones potentially totaling up to $247.0 million for each product developed by us that utilizes PeptiDream's technology, as well as low-to-mid single digit royalties on sales, if any, of any such products.

5. LIABILITY RELATED TO THE SALE OF FUTURE ROYALTIES

In April 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, 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 $500.0 million in September 2021.

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, 2021, 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 Leqvio global net revenue 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, 2021, the carrying value of the liability related to the sale of future royalties was $1.19 billion, net of closing costs of $11.6 million. The carrying value of the liability related to the sale of future royalties approximates fair value as of December 31, 2021 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.

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

Carrying value as of January 1, 2020	$ —
Sale of future royalties	1,000,000
Interest expense recognized	84,496
Capitalized closing costs	(12,955)
Carrying value as of December 31, 2020	1,071,541
Interest expense recognized	116,940
Payments	(378)
Carrying value as of December 31, 2021	$ 1,188,103

6. OTHER BALANCE SHEET DETAILS

Inventory

The components of inventory are summarized as follows:

	As of December 31,	
(In thousands)	2021	2020
Raw materials	$ 14,754	$ 63,460
Work in process	100,942	16,149
Finished goods	7,005	12,693
Total inventory	$ 122,701	$ 92,302

As of December 31, 2021 and 2020, we had $36.3 million and $17.1 million of long-term inventory, respectively, included within other assets in our consolidated balance sheet as we anticipate it being consumed beyond our normal operating cycle. As of December 31, 2021, we had $7.1 million of capitalized inventory produced for commercial sale for products awaiting regulatory approval. As of December 31, 2020, 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)	2021	2020
Buildings	$ 262,637	$ 262,637
Leasehold improvements	152,045	149,505
Construction in progress	80,753	28,005
Laboratory equipment	61,351	48,930
Manufacturing equipment	43,739	41,089
Computer equipment and software	21,885	19,064
Furniture and fixtures	10,883	11,066
Land	9,080	9,080
	642,373	569,376
Less: accumulated depreciation	(140,415)	(104,347)
Total	$ 501,958	$ 465,029

Accrued Expenses

Accrued expenses consist of the following:

	As of December 31,	
(In thousands)	2021	2020
Product rebates and discounts	$ 131,279	$ 94,242
Compensation and related	93,583	97,433
Pre-clinical, clinical trial and manufacturing	83,534	46,506
Licensing and collaboration agreements	22,843	15,424
Consulting and professional services	17,784	11,501
Contingent liabilities	—	41,216
Other	46,151	49,587
Total	$ 395,174	$ 355,909

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)	2021	2020	2019
Cash and cash equivalents	$ 819,975	$ 496,580	$ 547,178
Total restricted cash included in other assets	2,178	2,466	2,450
Total cash, cash equivalents, and restricted cash shown in the consolidated statements of cash flows	$ 822,153	$ 499,046	$ 549,628

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 Gains (Losses) from Debt Securities	Foreign Currency Translation Adjustment	Total Accumulated Other Comprehensive (Loss) Income
Balance as of December 31, 2019	$ (32,792)	$ (3,520)	$ 137	$ (343)	$ (36,518)
Other comprehensive loss 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)
Other comprehensive income before reclassifications	—	899	—	11,398	12,297
Amounts reclassified from other comprehensive income	—	44	(1,978)	—	(1,934)
Net other comprehensive income (loss)	—	943	(1,978)	11,398	10,363
Balance as of December 31, 2021	$ (32,792)	$ (2,811)	$ (1,630)	$ 3,974	$ (33,259)

7. CREDIT AGREEMENT

In April 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 of $700.0 million. The Tranche 1 Loan of $200.0 million, the Tranche 2 loan of $250.0 million and the Tranche 3 Loan of $250.0 million were drawn as of December 31, 2020, June 30, 2021, and December 31, 2021 respectively, and are included in long-term debt in the consolidated balance sheets. In addition to the $700.0 million previously drawn under the Credit Agreement, we may also request an increase 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.

The Term Loans mature in December 2027. 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. As of December 31, 2021, we had elected a LIBOR Rate plus 7%, and paid $17.5 million in total funding fees in connection with such Term Loans. Our interest rate was 8% as of December 31, 2021 and 2020.

We are obligated to pay interest due on the Term Loans from 2021 through 2022 which will be calculated without regard to the Term Loans being prepaid. Any prepayments of Term Loans that occur between 2023 and 2025 are subject to a fee of up to 5% of the loan principal that is prepaid.

All obligations under the Credit Agreement are secured, subject to certain exceptions, by security interests in the following assets: (i) intellectual property owned by us relating to ONPATTRO, GIVLAARI and vutrisiran, (ii) the equity interests held by the Loan Parties in their subsidiaries, (iii) all of our ownership of the inclisiran royalty remaining after the royalty purchase under the Purchase Agreement, and (iv) 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, 2021 and 2020, we were in compliance with the applicable terms and conditions of the covenants under the Credit Agreement.

8. DEVELOPMENT DERIVATIVE LIABILITY

In August 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 zilebesiran (formerly 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 November 2021, Blackstone Life Sciences opted in to Phase 2 clinical trial funding of zilebesiran, committing to fund, upon meeting certain patient enrollment thresholds, up to $26.0 million. Furthermore, Blackstone Life Sciences has the right, but is not obligated, to fund up to $54.0 million for development costs related to a Phase 3 clinical trial of zilebesiran. 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 zilebesiran.

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 zilebesiran, 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 zilebesiran Phase 2 clinical trial, unless certain regulatory events affecting the continued development of zilebesiran occur. As consideration for Blackstone Life Sciences' funding for Phase 3 clinical development costs of zilebesiran, 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 zilebesiran 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 zilebesiran, 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 zilebesiran 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 change in fair value due to the remeasurement of the development derivative liability is recorded as other expense on our consolidated statements of operations and comprehensive loss.

As of December 31, 2021 and 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 (14%), and (v) Blackstone Life Sciences' cost of borrowing (4%).

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

Carrying value as of January 1, 2020	$ —
Amount received under the Funding Agreement	8,400
Loss recorded from remeasurement	17,185
Carrying value as of December 31, 2020	25,585
Amount received under the Funding Agreement	19,600
Loss recorded from remeasurement	38,433
Carrying value as of December 31, 2021	$ 83,618

9. FAIR VALUE MEASUREMENTS

The following tables present information about our financial assets and liabilities 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, 2021	Quoted Prices in Active Markets (Level 1)	Significant Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial assets				
Cash equivalents:				
Money market funds	$ 255,869	$ 255,869	$ —	$ —
U.S. treasury securities	54,998	—	54,998	—
Marketable debt securities:				
U.S. treasury securities	1,030,578	—	1,030,578	—
Corporate notes	253,239	—	253,239	—
U.S. government-sponsored enterprise securities	177,741	—	177,741	—
Commercial paper	78,543	—	78,543	—
Certificates of deposit	7,501	—	7,501	—
Municipal securities	1,015	—	1,015	—
Marketable equity securities	66,972	66,972	—	—
Restricted cash (money market funds)	1,195	1,195	—	—
Total financial assets	$ 1,927,651	$ 324,036	$ 1,603,615	$ —
Financial liabilities				
Development derivative liability	$ 83,618	$ —	$ —	$ 83,618

(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:				
Money market funds	$ 75,726	$ 75,726	$ —	$ —
U.S. treasury securities	20,000	—	20,000	—
Marketable debt securities:				
U.S. treasury securities	1,087,968	—	1,087,968	—
U.S. government-sponsored enterprise securities	245,214	—	245,214	—
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

For the year ended December 31, 2021, 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, 2021 and 2020 is subject to variable interest rates, which are based on current market rates, and as such, approximates fair value.

10. MARKETABLE DEBT SECURITIES

The following tables summarize our marketable debt securities:

	As of December 31, 2021			
(In thousands)	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
U.S. treasury securities	$ 1,086,232	$ 6	$ (662)	$ 1,085,576
Corporate notes	253,926	1	(688)	253,239
U.S. government-sponsored enterprise securities	178,027	2	(288)	177,741
Commercial paper	78,543	—	—	78,543
Certificates of deposit	7,501	—	—	7,501
Municipal securities	1,016	—	(1)	1,015
Total	$ 1,605,245	$ 9	$ (1,639)	$ 1,603,615

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

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

(In thousands)	December 31, 2021	December 31, 2020
Cash and cash equivalents	$ 54,998	$ 20,000
Marketable debt securities	1,548,617	1,333,182
Total	$ 1,603,615	$ 1,353,182

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, 2021.

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, 2021.

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, 2021.

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 $59.5 million, $50.7 million and $52.4 million for the years ended December 31, 2021, 2020 and 2019, 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, 2021:

(In thousands)	Year Ended December 31, 2021	Year Ended December 31, 2020
Operating lease cost	$ 45,359	$ 42,271
Variable lease cost	18,271	11,049
Total	$ 63,630	$ 53,320

Short-term lease costs were not material for the years ended December 31, 2021 and 2020.

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 $41.9 million and $38.0 million for the years ended December 31, 2021 and 2020, respectively. The weighted-average remaining lease term and weighted-average discount rate for all leases as of December 31, 2021 was 11 years and 8%, respectively, and as of December 31, 2020 was 12 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, 2021 were as follows, in thousands:

Year Ending December 31	
2022	$ 41,783
2023	47,188
2024	44,421
2025	42,936
2026	40,246
2026 and thereafter	287,013
Total undiscounted lease liability	503,587
Less imputed interest	(181,692)
Total discounted lease liability	$ 321,895
Current operating lease liability	$ 40,548
Non-current operating lease liability	281,347
Total	$ 321,895

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, 2021, our commitments over the next five years to make fixed and cancellable payments under existing license agreements were not material.

Legal Matters

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.

Securities Litigation

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 Supreme Court of the State of New York entered a Decision and Order denying defendants' motion to dismiss. In November 2020, defendants filed a notice of appeal of the Supreme Court's decision to the Appellate Division of the Supreme Court of the State of New York for the First Department. In April 2021, the First Department entered a Decision and Order affirming in part and reversing in part the Supreme Court's decision. In June 2021, defendants filed a motion in the First Department seeking reargument or, in the alternative, for leave to appeal to the New York Court of Appeals. In August 2021, the parties reached an agreement in principle to resolve the matter. A hearing is scheduled for April 12, 2022 in the Supreme Court of the State of New York regarding final approval of the settlement. Proceedings in the First Department are adjourned until February 2022, subject to further adjournment, pending final approval of any settlement.

Government Investigation

We have previously disclosed that, on or about April 9, 2021, we received a subpoena from the U.S. Department of Justice, U.S. Attorney's Office for the District of Massachusetts, requiring production of documents pertaining to our marketing and promotion of ONPATTRO (patisiran) in the U.S. We are cooperating with the U.S. Attorney's Office and producing documents in response to the subpoena. Current and former officers and employees also have received subpoenas in connection with the preservation and production of related materials. Given the ongoing nature of the investigation, it is possible that the U.S. Attorney's Office for the District of Massachusetts or other government entities may request other information from, or issue other subpoenas, findings or similar documents to, us, our related entities and their respective directors, officers and employees. In light of the relatively early stage and ongoing nature of the investigation, no determination has been made that a loss, if any, arising from this matter is probable or that the amount of any such loss, or range of loss, is reasonably estimable. We also previously disclosed that since learning of this federal government investigation, our nominating and corporate governance committee is directing our review of and response to the matter.

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 or other legal proceedings. In addition, we have agreed to indemnify our officers and directors for expenses, judgments, fines, penalties, excise taxes, and settlement amounts paid in connection with any threatened, pending or completed litigation proceedings, including, for example, the current government investigation, in which an officer or director was, is or will be involved as a party, on account of such person's status as an officer or director, or by reason of any action taken by the officer or director while acting in such capacity, subject to certain limitations. These indemnification costs are charged to selling, general and administrative expense.

Our maximum potential future liability under any such indemnification provisions is uncertain. 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, 2021 or 2020.

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, 2021 and 2020, 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, 2021, an aggregate of 18,863,133 shares of common stock were reserved for issuance under our stock plans, including outstanding stock options to purchase 10,015,050 shares of common stock, 1,209,560 outstanding restricted stock units, 6,802,466 of common stock available for additional equity awards and 836,057 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)	**2021**	**2020**	**2019**
Research and development	$ 68,415	$ 60,464	$ 88,930
Selling, general and administrative	97,302	79,409	85,911
Total	$ 165,717	$ 139,873	$ 174,841

The following table summarizes stock-based compensation expense:

	Year Ended December 31,		
(In thousands)	**2021**	**2020**	**2019**
Stock-based compensation expense by type of award:			
Time-based stock options	$ 118,635	$ 112,971	$ 99,097
Time-based restricted stock units	4,231	6,909	2,351
Performance-based restricted stock units	39,943	11,162	22,123
Other equity programs	6,235	9,402	54,673
Less: Stock-based compensation expense capitalized to inventory	(3,327)	(571)	(3,403)
Total	$ 165,717	$ 139,873	$ 174,841

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, 2021	
	Unrecognized Expense, Net of Estimated Forfeitures (in thousands)	**Weighted-average Recognition Period (in years)**
Type of award:		
Time-based stock options	$ 181,281	2.40
Time-based restricted stock units	$ 7,439	1.70
Performance-based restricted stock units	$ —	*
Other equity programs	$ 9,060	2.75

* 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,		
	2021	2020	2019
Risk-free interest rate	0.4 - 1.4%	0.3 - 1.7%	1.4 - 2.6%
Expected dividend yield	—	—	—
Expected option life	5.4 - 6.8 years	5.4 - 7.2 years	5.6 - 7.3 years
Expected volatility	58 - 63%	61 - 63%	63 - 66%

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, 2020	10,068	$ 88.18		
Granted	1,893	154.31		
Exercised	(2,534)	76.40		
Cancelled	(587)	115.95		
Outstanding as of December 31, 2021	8,840	$ 103.87	6.21	$ 582,964
Exercisable as of December 31, 2021	5,223	$ 87.39	4.93	$ 429,323
Vested or expected to vest as of December 31, 2021	8,494	$ 102.59	6.13	$ 570,805

The weighted-average fair value of stock options granted was $82.59, $66.28 and $49.27 per share for the years ended December 31, 2021, 2020 and 2019, respectively. The intrinsic value of stock options exercised was $247.8 million, $177.8 million and $55.4 million for the years ended December 31, 2021, 2020 and 2019, respectively. We satisfy stock option exercises with newly issued shares of our common stock.

Performance-Based Stock Options

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, 2020	1,625	$ 91.35		
Granted	—	—		
Exercised	(446)	88.62		
Cancelled	(4)	119.13		
Outstanding as of December 31, 2021	1,175	$ 92.31	3.65	$ 90,823
Exercisable as of December 31, 2021	1,175	$ 92.31	3.65	$ 90,823

During the years ended December 31, 2021, 2020 and 2019, there were 197,102, 0 and 889,896 performance-based stock options that vested, respectively. The intrinsic value of performance-based stock options exercised was $40.2 million, $34.1 million and $11.0 million for the years ended December 31, 2021, 2020 and 2019, 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 granted under our equity plans, excluding performance-based restricted stock units:

	Number of Units (in thousands)	Weighted-average Grant Date Fair Value
Outstanding as of December 31, 2020	117	$ 83.66
Awarded	79	159.18
Released	(110)	81.94
Cancelled	(11)	131.01
Outstanding as of December 31, 2021	75	$ 158.87

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, 2020	1,043	$ 107.26
Awarded	813	153.76
Released	(544)	97.73
Cancelled	(176)	126.45
Outstanding as of December 31, 2021	1,136	$ 143.13

The performance-based restricted stock units granted in 2021 and 2020 will vest upon the later of the one-year anniversary of the date of grant and the achievement of specific clinical development, regulatory, commercial and/or financial performance 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 2017, our stockholders approved the Amended and Restated ESPP. In 2020, our stockholders approved an amendment to the Amended and Restated ESPP, to increase the number of shares authorized for issuance 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 124,101 and 129,394 shares during the years ended December 31, 2021 and 2020, respectively.

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,		
	2021	2020	2019
Risk-free interest rate	0.03% - 0.06%	0.1% - 0.1%	1.6% - 2.4%
Expected dividend yield	—	—	—
Expected option life	6 months	6 months	6 months
Expected volatility	41% - 46%	40% - 50%	37% - 56%

15. INCOME TAXES

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

(In thousands)	2021	2020	2019
Domestic	$ (794,729)	$ (682,859)	$ (597,602)
Foreign	(57,415)	(172,741)	(287,651)
Loss before income taxes	$ (852,144)	$ (855,600)	$ (885,253)

The provision for income taxes consisted of the following:

	Year Ended December 31,		
(In thousands)	2021	2020	2019
Current provision:			
Domestic	$ 293	$ 61	$ (394)
Foreign	3,154	5,837	3,232
Total current provision	3,447	5,898	2,838
Deferred benefit:			
Domestic	—	393	394
Foreign	(2,767)	(3,610)	(2,369)
Total deferred benefit	(2,767)	(3,217)	(1,975)
Total provision for income taxes	$ 680	$ 2,681	$ 863

During the year ended December 31, 2021, we recorded a net provision for income taxes of $0.7 million. This is primarily comprised of $3.2 million of foreign current provision offset by $2.8 million of deferred provision, primarily related to foreign jurisdictions.

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 asset are as follows:

	As of December 31,	
(In thousands)	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	$ 745,985	$ 537,382
Research and development and other credit carryforwards	342,431	301,792
Sale of future royalties	302,217	259,014
Lease liability	71,859	70,402
Deferred revenue	76,612	84,946
Deferred compensation	59,349	67,530
Intangible assets	302,121	148,168
Other	48,242	32,725
Total deferred tax assets	1,948,816	1,501,959
Deferred tax liabilities:		
Property, plant and equipment, net	(13,170)	(10,812)
Unrealized gain on marketable securities	(16,693)	(12,766)
Right of use assets	(50,562)	(50,323)
Deferred revenue tax accounting method change	(50,380)	(71,812)
Deferred tax asset valuation allowance	(1,808,992)	(1,349,729)
Net deferred tax asset	$ 9,019	$ 6,517

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

	Year Ended December 31,		
(In thousands)	2021	2020	2019
At U.S. federal statutory rate	21.0 %	21.0 %	21.0 %
State taxes, net of federal effect	5.2	4.5	3.6
Stock-based compensation	4.6	2.2	—
Tax credits	4.5	3.3	3.7
Other permanent items	(1.0)	(1.5)	(0.3)
Foreign rate differential	(1.7)	(3.5)	(6.9)
Internal reorganization of certain intellectual property rights	20.1	12.3	—
Other	(0.1)	(2.7)	(0.1)
Revaluation of deferred due to rate change	1.1	—	—
Valuation allowance	(53.8)	(35.9)	(21.0)
Effective income tax rate	(0.1)%	(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 $459.3 million, $303.7 million and $185.9 million for the years ended December 31, 2021, 2020 and 2019, respectively. The increase in our valuation allowance is primarily due to additional net operating losses for the years ended December 31, 2021 and 2019 and primarily due to the liability related to the sale of future royalties for the year ended December 31, 2020.

As of December 31, 2021, we had federal and state net operating loss carryforwards of $2.8 billion and $2.5 billion, respectively, to reduce future taxable income. Federal NOLs of $1.1 billion, generated before 2018, will begin expiring in varying amounts through 2037 unless utilized. The remaining federal NOLs of $1.7 billion, generated after 2017, will be carried forward indefinitely and could be used to offset up to 100% of taxable income of each future tax year for tax years before January 1, 2021 and up to 80% of taxable income in all other future tax years. As of December 31, 2021, we had federal and state research and development, including Orphan Drug, and state investment tax credit carryforwards of $312.2 million and $50.5 million, respectively, available to reduce future tax liabilities that expire at various dates through 2041. 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, 2021. 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 and ultimately sustained upon challenge by a taxing authority based upon its technical merits and subject to certain recognition and measurement criteria. 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, 2021 and 2020.

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, 2021, 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 2018 through 2021 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 2018 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 $4.3 million and $5.2 million as of December 31, 2021 and 2020, respectively, and is recorded in other liabilities on the consolidated balance sheet. The total net periodic benefit cost for the years ended December 31, 2021, 2020 and 2019 were not material.

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, 2021. 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, 2021, 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, 2021. 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, 2021, 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, 2021 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, 2021 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

Not applicable.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

Incorporated by reference from the information in our Proxy Statement for our 2022 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 2022 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 2022 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.

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, 2021. 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.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

Incorporated by reference from the information in our Proxy Statement for our 2022 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 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year to which this Annual Report on Form 10-K relates.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) (1) Financial Statements

The following consolidated financial statements are filed as part of this report under "Item 8 — Financial Statements and Supplementary Data:"

(a) (2) List of Schedules

All schedules to the consolidated financial statements are omitted as the required information is either inapplicable or presented in the consolidated financial statements.

(a) (3) List of Exhibits

Exhibit No.	Exhibit
2.1*†	Stock Purchase Agreement dated as of January 10, 2014 by and among the Registrant, Sirna Therapeutics, Inc., Merck Sharp & Dohme Corp., and solely for the purposes of certain specified provisions, Merck & Co., Inc. (filed as Exhibit 2.1 to the Registrant's Quarterly Report on Form 10-Q filed on May 9, 2014 (File No. 001-36407) for the quarterly period ended March 31, 2014 and incorporated herein by reference)
3.1	Restated Certificate of Incorporation of the Registrant (filed as Exhibit 3.1C to the Registrant's Current Report on Form 8-K filed on April 26, 2019 (File No. 001-36407) and incorporated herein by reference)
3.2	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#	Forms of Nonstatutory Stock Option Agreements under 2018 Stock Incentive Plan, as amended
10.12**#	Forms of Stock Unit Award Agreements under 2018 Stock Incentive Plan, as amended
10.13**	Amended and Restated Annual Incentive Program, as amended (filed as Exhibit 10.12 to the Registrant's Annual Report on Form 10-K filed on February 11, 2021 (File No. 001-36407) for the year ended December 31, 2020 and incorporated herein by reference)
10.14**	Employment Agreement between the Registrant and Dr. Yvonne L. Greenstreet dated December 14, 2021 (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on December 20, 2021 (File No. 001-36407) and incorporated herein by reference)
10.15**	Letter Agreement between the Registrant and John M. Maraganore, Ph.D. dated October 26, 2021 (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on October 28, 2021 (File No. 001-36407) and incorporated herein by reference)
10.16**	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)
10.17**	Letter Agreement between the Registrant and Laurie B. Keating dated September 6, 2021 (filed as Exhibit 10.1 to Registrant's Quarterly Report on Form 10-Q filed on October 28, 2021 (File No. 001-36407) for the quarterly period ended September 30, 2021 and incorporated herein by reference)
10.18**	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)
10.19**	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)
10.20**	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)
10.21**	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)
10.22	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)
10.23	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
10.24	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)
10.25	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)
10.26	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)
10.27	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)
10.28	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)
10.29†	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)
10.30	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)
10.31	Second Amendment to Lease entered into as of April 28, 2021 by and between BMR-Fresh Pond Research Park LLC and the Registrant (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on August 3, 2021 (File No. 001-36407) for the quarterly period ended June 30, 2021 and incorporated herein by reference)
10.32	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)
10.33	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)
10.34	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)
10.35	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)
10.36	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)
10.37	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)

Exhibit No.	Exhibit
10.38†	Co-exclusive License Agreement between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam U.S., Inc. dated December 20, 2002, as amended by Amendment dated July 8, 2003 together with Indemnification Agreement by and between Garching Innovation GmbH (now known as Max Planck Innovation GmbH) and Alnylam Pharmaceuticals, Inc. effective April 1, 2004 (filed as Exhibit 10.19 to the Registrant's Registration Statement on Form S-1 (File No. 333-113162) and incorporated herein by reference)
10.39†	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)
10.40†	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)
10.41	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)
10.42	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)
10.43	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)
10.44†	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)
10.45†	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)
10.46†	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)
10.47†	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)
10.48†	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)
10.49†	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)

Exhibit No.	Exhibit
10.50	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)
10.51†	Investor Agreement dated as of April 8, 2019 by and between the Registrant and Regeneron Pharmaceuticals, Inc. (filed as Exhibit 10.7 to the Registrant's Quarterly Report on Form 10-Q filed on August 6, 2019 (File No. 001-36407) for the quarterly period ended June 30, 2019 and incorporated herein by reference)
10.52†	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)
10.53†	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)
10.54	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)
10.55†	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)
10.56†	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)
10.57†	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)
10.58†	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)
10.59†	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)
10.60†	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)
10.61†	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)
10.62†	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)

Exhibit No.	Exhibit
10.63†	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)
10.64†	Manufacturing Services Agreement effective as of March 28, 2018 by and between the Registrant and Agilent Technologies, Inc. (filed as Exhibit 10.4 to the Registrant's Quarterly Report on Form 10-Q filed on May 4, 2018 (File No. 001-36407) for the quarterly period ended March 31, 2018 and incorporated herein by reference)
10.65†	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)
10.66*	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)
10.67*	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)
10.68	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)
10.69*†	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)
10.70*†#	Amendment No. 1 to Co-Development Agreement between the Registrant and BXLS V Bodyguard – PCP L.P. and BXLS Family Investment Partnership V – ESC L.P. dated November 23, 2021
10.71†	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

Exhibit No.	Exhibit
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 this exhibit 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

None.

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 10, 2022.

ALNYLAM PHARMACEUTICALS, INC.

By: /s/ Yvonne L. Greenstreet, MBChB
Yvonne L. Greenstreet, MBChB
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 10, 2022.

Name	Title
/s/ Yvonne L. Greenstreet, MBChB Yvonne L. Greenstreet, MBChB	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

Alnylam Leadership

MANAGEMENT TEAM

Yvonne L. Greenstreet, MBChB, MBA
Chief Executive Officer

Akshay K. Vaishnaw, MD, PhD
President

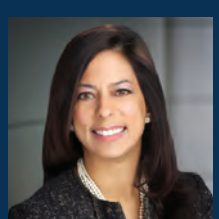
Pushkal P. Garg, MD
Chief Medical Officer and EVP, Development & Medical Affairs

Jeffrey V. Poulton, MBA
Chief Financial Officer

Kelley Boucher
Chief Human Resource Officer

Al Boyle, PhD
Chief Technical Operations & Quality Officer

Tolga Tanguler, MBA
Chief Commercial Officer



Indrani Franchini, JD
Chief Legal Officer

BOARD OF DIRECTORS

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

Dennis A. Ausiello, MD
Director of the Center for Assessment Technology and Continuous Health; 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 and Rani Therapeutics and formerly served as director of Pfizer Inc.

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.

Yvonne Greenstreet, MBChB, MBA
Chief Executive Officer of Alnylam; member of the Board of Directors of Pacira BioSciences, Inc., and The American Funds; Scientific Advisory Committee of the Bill and Melinda Gates Foundation; member of the Discovery Council of Harvard Medical School; member of Biotechnology Industry Organization Health Section Governing Board.

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

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; cofounder and board member of SAGE Therapeutics; trustee for the Foundation for the National Institute of Mental Health; former President of the Lilly Research Laboratories of Eli Lilly and Company; former Scientific Director of the National Institute of Mental Health; 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; former President and Chief Operating Officer of Blue Cross Blue Shield of Minnesota; Director of Myriad Genetics.

Amy W. Schulman, JD, Lead Independent Director
Managing Partner, Polaris Partners; cofounder, Executive Chair, and former Chief Executive Officer of Lyndra Therapeutics; Chair of SQZ Biotech; 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, Koch Institute for Integrative Cancer Research, MIT; Founding Director of McGovern Institute for Brain Research, MIT; Nobel Laureate; Founder of Alnylam; cofounder 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.

Connect with Us

Corporate Headquarters
Alnylam Pharmaceuticals, Inc.
Henri A. Termeer Square
675 West Kendall Street
Cambridge, MA 02142
USA
+1 617-551-8200
alnylam.com

Stock Symbol
ALNY (Nasdaq)

Transfer Agent
First Class/Registered/Certified Mail:
Computershare Investor Services
PO BOX 5050005
Louisville, KY 40233-50005
USA

Courier Services
Computershare Investor Services
462 South 4th Street, Suite 1600
Louisville, KY 40202
USA

Corporate Counsel
Goodwin Procter LLP
100 Northern Avenue
Boston, MA 02210
USA
+1 617-570-1000

Independent Auditors
PricewaterhouseCoopers LLP
101 Seaport Boulevard, Suite 500
Boston, MA 02210
USA
+1 617-530-5000

@AlnylamPharma
@Alnylam
Alnylam Pharmaceuticals
Alnylam Pharmaceuticals

Alnylam®@20