

IONIS[™]

2020 | ANNUAL
REPORT

**Pioneering
New Markets**

—
**Changing the
Standard
of Care**



**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION**
Washington, DC 20549

FORM 10-K

- ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2020
- TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from _____ to _____
- Commission file number 000-19125

Ionis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

33-0336973
(IRS Employer
Identification No.)

2855 Gazelle Court, Carlsbad, CA
(Address of Principal Executive Offices)

92010
(Zip Code)

760-931-9200
(Registrant's telephone number, including area code)

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

Title of each class	Trading symbol	Name of each exchange on which registered
Common Stock, \$.001 Par Value	"IONS"	The Nasdaq Stock Market LLC

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

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

Indicate by check 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 Securities Act.

Indicate by check mark whether the registrant has filed a report on and attestation to its management assessment of the effectiveness of its internal controls 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

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

The approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on The Nasdaq Global Select Market was \$6,748,320,336 as of June 30, 2020.*

The number of shares of voting common stock outstanding as of February 18, 2021 was 140,862,211.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 23, 2021 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 2, 2021 are incorporated by reference into Part III of this Report.

* Excludes 25,033,497 shares of common stock held by directors and officers and by stockholders whose beneficial ownership is known by the Registrant to exceed 10 percent of the common stock outstanding at June 30, 2020. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

FORWARD-LOOKING STATEMENTS

This report on Form 10-K and the information incorporated herein by reference includes forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen) and our technologies and products in development, including the business of Akcea Therapeutics, Inc., our wholly owned subsidiary. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact of COVID-19 could have on our business, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report on Form 10-K, including those identified in Item 1A entitled “Risk Factors”. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

In this report, unless the context requires otherwise, “Ionis,” “Company,” “we,” “our,” and “us” refers to Ionis Pharmaceuticals, Inc. and its subsidiaries.

SUMMARY OF RISK FACTORS

There are a number of risks related to our business and our securities. Below is a summary of material factors that make an investment in our securities speculative or risky. Importantly, this summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factor summary, as well as other risks that we face, can be found in this report on Form 10-K in Item 1A entitled “Risk Factors.”:

- the impact on our operations and financial condition from the effects of the current COVID-19 pandemic;
- our ability to generate substantial revenue from the sale of our medicines;
- our and our partners’ ability to compete effectively;
- the availability of adequate coverage and payment rates for our medicines;
- our ability to successfully manufacture our medicines;
- our ability to successfully develop and obtain marketing approvals for our medicines;
- our ability to secure and maintain effective corporate partnerships;
- our ability to sustain cash flows and achieve consistent profitability;
- our ability to protect our intellectual property; and
- our ability to maintain the effectiveness of our personnel.

TRADEMARKS

“Ionis,” the Ionis logo, and other trademarks or service marks of Ionis Pharmaceuticals, Inc. appearing in this report are the property of Ionis Pharmaceuticals, Inc. “Akcea,” the Akcea logo, and other trademarks or service marks of Akcea Therapeutics, Inc. appearing in this report are the property of Akcea Therapeutics, Inc, Ionis’ wholly owned subsidiary. This report contains additional trade names, trademarks and service marks of others, which are the property of their respective owners. Solely for convenience, trademarks and trade names referred to in this report may appear without the ® or TM symbols.

CORPORATE INFORMATION

We incorporated in California in 1989 and in January 1991 we changed our state of incorporation to Delaware. In December 2015, we changed our name to Ionis Pharmaceuticals, Inc. from Isis Pharmaceuticals, Inc. Our principal offices are in Carlsbad, California. In December 2014, we formed Akcea Therapeutics, Inc., as a Delaware corporation, with its principal office in Boston, Massachusetts. Prior to Akcea's initial public offering, or IPO, in July 2017, we owned 100 percent of Akcea's stock. In October 2020, we acquired the remaining shares of Akcea.

We make available, free of charge, on our website, www.ionispharma.com, our reports on Forms 10-K, 10-Q, 8-K and amendments thereto, as soon as reasonably practical after we file such materials with the Securities and Exchange Commission. Periodically, we provide updates about the company in the Newsroom section of the Investors & Media page of our website. Any information that we include on or link to our website is not a part of this report or any registration statement that incorporates this report by reference.

IONIS PHARMACEUTICALS, INC.
FORM 10-K
For the Fiscal Year Ended December 31, 2020
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PART I

Item 1. Business

Overview

We are a leader in RNA-targeted therapy and believe our medicines are pioneering new markets, changing standards of care and transforming the lives of people with devastating diseases. Our clinical pipeline of potential first-in-class and/or best-in-class medicines address a broad range of diseases. We are primarily focused on two core franchises: neurology and cardiometabolic. Our commercial products SPINRAZA, TEGSEDI and WAYLIVRA, are approved in major markets around the world. Within our late-stage pipeline, we have six Phase 3 studies underway with five medicines: tofersen for SOD1-ALS, tominersen for Huntington's disease, IONIS-TTR-L_{Rx} for transthyretin, or TTR, amyloidosis, IONIS-APOCIII-L_{Rx} for familial chylomicronemia syndrome, or FCS, and pelacarsen for lipoprotein(a), or Lp(a), driven cardiovascular disease.

2020 was a transformational year for Ionis. With new leadership and a new strategy to commercialize medicines from our wholly owned pipeline, we took important steps towards our goal of becoming one of the most successful biotechnology companies. We invested in our commercial capabilities and expanded our wholly owned pipeline, accelerated by the acquisition of Akcea Therapeutics, or the Akcea Acquisition. As one company, we believe we are stronger and more efficient, with enhanced ability to achieve even greater future success. We initiated two Phase 3 studies and reported clinical proof-of-concept results from six medicines. We also advanced our mid-stage pipeline by initiating more than ten Phase 2 studies, including four studies with our wholly owned medicines. In 2020, we also broadened the scope of our technology by demonstrating we could safely and effectively deliver an antisense medicine to the lungs. We accomplished all this and achieved our 2020 financial guidance, with revenues of \$729.3 million and a year-end cash balance of \$1.9 billion, even in the challenging COVID-19 pandemic environment.

Our multiple sources of revenue provide us with substantial financial strength. Our financial strength enables us to execute on our capital allocation strategy, which is focused on internal investment in three key areas: our wholly owned pipeline, building our commercial capabilities and broadening the reach of our technology. We believe investing in these areas moves us closer to our goal of 12 or more marketed products in 2026 and will drive the greatest value for patients and shareholders.

Commercial Medicines

SPINRAZA is the global foundation-of-care for the treatment of patients of all ages with spinal muscular atrophy, or SMA, a progressive, debilitating and often fatal genetic disease. Biogen, our partner responsible for commercializing SPINRAZA worldwide, reported that as of December 31, 2020, over 11,000 patients were on SPINRAZA therapy in markets around the world. SPINRAZA is approved in over 50 countries with formal reimbursement in over 40 countries. From inception through December 31, 2020, we have earned \$1.3 billion in revenues from our SPINRAZA collaboration, including more than \$930 million in royalties on sales of SPINRAZA.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in the U.S., Europe, Canada and Brazil for the treatment of patients with polyneuropathy caused by hereditary TTR amyloidosis, or hATTR, a debilitating, progressive, and fatal disease. As of December 31, 2020, TEGSEDI was commercially available in 15 countries. In 2021, we began selling TEGSEDI in Europe through a distribution model with Swedish Orphan Biovitrum AB, or Sobi. In Latin America, PTC Therapeutics International Limited, or PTC, through its exclusive license agreement with us, is commercializing TEGSEDI in Brazil and is working towards access in additional Latin American countries.

WAYLIVRA is a once weekly, self-administered, subcutaneous medicine that received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis. We launched WAYLIVRA in the EU in the third quarter of 2019. In 2021, we began selling WAYLIVRA through a distributor, Sobi. Through our exclusive license agreement with PTC, we are working to expand access to WAYLIVRA across Latin America, beginning in Brazil. In the second quarter of 2020, PTC submitted the WAYLIVRA marketing application for approval in Brazil to the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária), or ANVISA.

Medicines in Phase 3 Studies

We advanced our pipeline of medicines that we believe will pioneer new markets and change standards of care. Our Phase 3 medicines include:

- Tofersen: Biogen completed enrollment in the VALOR Phase 3 study in patients with SOD1-ALS in December 2020
- Tominersen: Roche completed enrollment of the GENERATION HD1 Phase 3 study for tominersen in April 2020
- IONIS-TTR-L_{Rx}: Enrollment ongoing in both the NEURO-TTRansform and the CARDIO-TTRansform Phase 3 studies
- IONIS-APOCIII-L_{Rx}: We initiated the BALANCE Phase 3 study in patients with FCS in December 2020
- Pelacarsen: Novartis began enrollment in the Lp(a)HORIZON Phase 3 cardiovascular outcome study and the U.S. Food and Drug Administration, or FDA, granted pelacarsen Fast Track Designation as a potential treatment for people at significant risk for cardiovascular disease due to elevated levels of Lp(a).

COVID-19

As a company focused on improving the health of people around the world, our priority during the COVID-19 pandemic is the safety of our employees, their families, the healthcare workers who work with us and the patients who rely on our medicines. We are also focused on maintaining the quality of our studies and minimizing the impact to timelines. While the COVID-19 pandemic has impacted some areas of our business, we believe our mitigation efforts and financial strength will enable us to continue to manage through the pandemic and execute on our strategic initiatives. Because the situation is extremely fluid, we are continuing to evaluate the impact COVID-19 could have on our business, including the impact on our commercial products and the medicines in our pipeline.

Our Marketed Medicines – Transformational Medicines Bringing Value to Patients Today

SPINRAZA – SPINRAZA (nusinersen) injection for intrathecal use is a survival motor neuron-2, or SMN2, directed antisense medicine indicated for the treatment of SMA in pediatric and adult patients.

SPINRAZA continues to demonstrate substantial benefit in SMA patients of all ages, supporting its position as a global foundation of care for the treatment of SMA. Biogen, our worldwide commercial partner, reported that as of December 31, 2020, there were more than 11,000 patients on SPINRAZA therapy with approval in over 50 countries around the world.

SMA is characterized by loss of motor neurons in the spinal cord and lower brain stem, resulting in severe and progressive muscular atrophy and weakness. Ultimately, if untreated, individuals with the most severe type of SMA, infantile-onset, or Type 1, SMA, can become paralyzed and have difficulty performing the basic functions of life, like breathing and swallowing. Due to a loss of, or defect in, the *SMN1* gene, people with SMA do not produce enough SMN protein, which is critical for the maintenance of motor neurons. The severity of SMA correlates with the amount of SMN protein a patient can produce on his/her own. Patients with Type 1 SMA produce very little SMN protein and do not achieve the ability to sit without support or live beyond two years without respiratory support. Patients with later-onset, or Type 2 or Type 3 SMA, suffer from less severe, but still life-altering, forms of SMA. These patients produce greater amounts of SMN protein, but also experience progressive degeneration due to the disease.

The approval of SPINRAZA was based on safety and efficacy data from multiple clinical studies, including two randomized, placebo-controlled Phase 3 studies, ENDEAR, in patients with infantile-onset SMA, and CHERISH, in patients with later-onset SMA as well as from SHINE, an ongoing open label extension, or OLE, study for patients with SMA who participated in prior SPINRAZA studies.

Biogen is conducting DEVOTE, a Phase 2/3 study evaluating the safety and potential to achieve increased efficacy with a higher dose of SPINRAZA compared to the currently approved dose. The DEVOTE study is enrolling SMA patients of all ages, including adults. We and Biogen believe that SPINRAZA's favorable long-term safety and tolerability profile observed in over 11,000 SMA patients of all ages, with some patients treated for up to 7 years, supports evaluation of higher SPINRAZA dosing.

In January 2021, Biogen initiated the global Phase 4 RESPOND study evaluating the benefit of SPINRAZA in infants and children with a suboptimal clinical response to the gene therapy, onasemnogene abeparvovec. RESPOND is a two-year, open-label study that Biogen is conducting at approximately 20 sites worldwide and is expecting to enroll approximately 60 children with SMA. The primary endpoint is the total score on the Hammersmith Infant Neurological Examination.

For over six years, Biogen has been conducting the Phase 2 open-label NURTURE study, the first study investigating a treatment targeting the underlying cause of SMA in infants with the genetic diagnosis of SMA (most likely to develop SMA Type 1 or 2) before onset of symptoms. Biogen published an interim analysis of the NURTURE data demonstrating SPINRAZA-treated infants achieved motor milestones in timelines more consistent with normal development than what is observed in the natural history of patients with Type 1 SMA. At the time of the interim analysis, all patients were alive and did not require respiratory intervention. All of the patients in the study were able to sit without support and 96 percent of the patients were able to walk either with assistance or independently. No new safety concerns were identified.

In November 2018, SPINRAZA was recognized with the International Prix Galien Best Biotechnology Product award. The prestigious honor marks the seventh Prix Galien award for SPINRAZA, following country recognitions in the U.S., Germany, Italy, Belgium-Luxembourg, the Netherlands and the U.K. The International Prix Galien award is given every two years by Prix Galien International Committee members in recognition of excellence in scientific innovation to improve human health.

TEGSEDI – TEGSEDI (inotersen) injection is an RNA-targeted medicine indicated for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. TEGSEDI is commercially available in 15 countries, including the U.S., many European countries, Canada and Latin America.

TTR amyloidosis is a systemic, progressive and fatal disease caused by the formation and aggregation of TTR amyloid deposits in various tissues and organs, including peripheral nerves, heart, intestinal track, and central nervous system. There are an estimated 250,000 people worldwide with TTR amyloidosis.

TTR amyloidosis that is the result of inherited mutations in the *TTR* gene is referred to as hATTR. There are an estimated 50,000 people worldwide with hATTR. There are two primary manifestations of hATTR: polyneuropathy and cardiomyopathy. Many people with hATTR often experience both manifestations, but often one manifestation or the other is diagnosed first and is more pronounced.

In people with hATTR, both the mutant and wild type, or wt, TTR protein builds up as fibrils in tissues, such as peripheral nerves, heart, gastrointestinal system, eyes, kidneys, central nervous system, thyroid and bone marrow. The presence of TTR protein fibrils interferes with the normal function of these tissues. As the TTR protein fibrils enlarge, more tissue damage occurs and the disease worsens, resulting in poor quality of life and eventually death. We designed TEGSEDI to reduce the production of the TTR protein, the underlying cause of hATTR.

People without mutations in the *TTR* gene can also develop ATTR, often referred to as wild-type, or wt-ATTR. This non-hereditary form of the disease results from normal, non-mutant, TTR protein forming fibrils, primarily in the heart. People with hATTR cardiomyopathy and wt-ATTR experience ongoing debilitating heart damage resulting in progressive heart failure, which results in death within three to five years from disease onset. It is estimated that more than 200,000 people worldwide have wt-ATTR.

TEGSEDI was recognized with the Prix Galien USA award for the Best Biotechnology Product in 2020. TEGSEDI is the second of our products to receive this prestigious honor.

The approvals of TEGSEDI were based on results from the Phase 3 NEURO-TTR study in patients with hATTR amyloidosis with stage 1 and stage 2 polyneuropathy. Results from that study demonstrated that patients treated with TEGSEDI experienced significant benefit compared to patients treated with placebo across both co-primary endpoints: the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy, or Norfolk QoL-DN, and modified Neuropathy Impairment Score +7, or mNIS+7, a measure of neuropathic disease progression. In July 2018, the final results from the NEURO-TTR pivotal study were published in *The New England Journal of Medicine*.

We also conducted an OLE study in patients with hATTR treated with TEGSEDI. This study was intended to evaluate the long-term efficacy and safety profile of TEGSEDI. We reported interim data from the study that

demonstrated continued efficacy in patients after two years and there were no new safety signals identified. Results also showed that patients who started treatment earlier achieved greater long-term disease stabilization compared to those who switched from placebo to TEGSEDI in the OLE study. The data from this study were published in *The European Journal of Neurology* in May 2020.

WAYLIVRA – WAYLIVRA (volanesorsen) is an antisense medicine indicated as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

WAYLIVRA is commercially available in six European countries. We plan to launch WAYLIVRA in Brazil through our exclusive license agreement with PTC, assuming approval.

FCS is a rare, genetic disease characterized by extremely elevated triglyceride levels that is estimated to affect 3,000 to 5,000 people worldwide. FCS can lead to many chronic health issues including severe, recurrent abdominal pain, fatigue, high risk of life-threatening pancreatitis and abnormal enlargement of the liver or spleen. In addition, people with FCS are often unable to work, adding to their disease burden. In severe cases, patients can have bleeding into the pancreas, serious tissue damage, infection and cyst formation, as well as damage to other vital organs such as the heart, lungs and kidneys.

WAYLIVRA reduces triglyceride levels by inhibiting the production of apolipoprotein C-III, or apoC-III, a protein that is a key regulator of triglyceride levels. People who have low levels of apoC-III or reduced apoC-III function have lower levels of triglycerides and a lower incidence of cardiovascular disease, or CVD. By inhibiting the production of apoC-III, WAYLIVRA is able to reduce triglyceride levels in people with high levels of triglycerides.

The conditional marketing authorization for WAYLIVRA is based on results from the Phase 3 APPROACH study, the ongoing APPROACH OLE study and supported by results from the Phase 3 COMPASS study. The pivotal APPROACH study was a one-year, randomized, placebo-controlled study in 66 patients with FCS (average baseline triglycerides of 2,209 mg/dL, or 25.0 mmol/L). The study achieved its primary endpoint of reduction in triglycerides at three months, with a 77 percent mean reduction in triglycerides, which translated into a 1,712 mg/dL (19.3 mmol/L) mean absolute triglyceride reduction in WAYLIVRA-treated patients. We observed 50 percent of treated patients achieved triglyceride levels below 500 mg/dL, a commonly accepted threshold for pancreatitis risk. In addition, treatment with WAYLIVRA was associated with a statistically significant reduced rate of pancreatitis attacks in the group of patients who had the highest incidence of pre-study pancreatitis and reduced abdominal pain in patients reporting pain before treatment in the study. In August 2019, the final results from the APPROACH pivotal study were published in *The New England Journal of Medicine*.

An OLE study is ongoing for patients with FCS who have completed or meet the study criteria for the APPROACH and COMPASS studies. Additionally, we have expanded access programs, or EAPs, for WAYLIVRA.

Drug Discovery and Development

Introduction to Drug Discovery

Proteins are essential working molecules in a cell. Almost all human diseases result from inappropriate protein production, improper protein activity or loss of a protein. Antisense medicines can modify the production of proteins by targeting RNAs. In this way, antisense medicines can inhibit the production of a disease-causing protein, modify the protein produced or increase the production of a protein that, when absent, causes diseases. Antisense medicines can also treat diseases by targeting and reducing RNAs that may be causing diseases (so called “toxic RNAs”). RNAs are naturally occurring molecules in the body that primarily act as messengers that carry the information the cell needs to produce proteins from the deoxyribonucleic acid, or DNA, to the protein making complex in the cell. When antisense medicines bind to the specific RNAs of a particular gene, they will ultimately alter the production of the protein encoded in the target gene or, in the case of disease-causing RNAs, degrade the toxic RNAs.

Our Development Projects

We are a leader in the discovery and development of antisense oligonucleotide medicines, or antisense medicines. By efficiently screening many targets in parallel to select the best candidates and applying our rational approach to selecting disease targets, we have built a robust portfolio of medicines designed to treat many serious diseases, such as cardiometabolic diseases, neurological diseases and others. We are developing antisense medicines for systemic and local delivery (e.g., subcutaneous, intrathecal, intraocular, oral and aerosol).

We plan to continue to add new investigational medicines to our pipeline creating opportunities to continue to generate substantial revenue. We also continue to improve our scientific understanding of our medicines, including how our medicines impact the biological processes of the diseases we target.

With our expertise in discovering and characterizing novel antisense medicines, our scientists can optimize the properties of our antisense medicines against each particular target. Our scientists have made significant advances in chemical modifications we use in our antisense medicines, such as with our Generation 2+ antisense medicines, which have increased potency and an improved side effect profile over our earlier generation medicines. Our scientists have further improved upon our second-generation chemistry with our Generation 2.5 chemistry, an advancement that further increases the potency of our medicines, which broadens the organs and tissues in which our medicines can work. We currently have 17 Generation 2.5 medicines in development, and we anticipate that more of our future medicines will incorporate our Generation 2.5 chemistry.

In addition to improving the chemical foundation of our medicines, we have also created LIgand-Conjugated Antisense, or LICA, technology, which we design to enhance the effective uptake and activity of our medicines in particular tissues. With our LICA technology we attach specific chemical structures or molecules to our antisense medicines. With our first LICA conjugate, a complex sugar-like molecule called N-acetylgalactosamine, or GalNac, we have shown an increase in medicinal potency of 20-30-fold for liver targets, compared to non-conjugated antisense medicines. We currently have 15 LICA medicines in development, including three LICA medicines currently in Phase 3 studies, pelacarsen, for CVD, IONIS-TTR-L_{Rx}, for all forms of ATTR and IONIS-APOCIII-L_{Rx} for FCS. We also have four investigational medicines that combine our Generation 2.5 chemistry and LICA technology.

We have utilized our chemistry advancements, such as Generation 2.5 and LICA, to expand the therapeutic and commercial opportunities of our pipeline. These advancements, along with the manufacturing and analytical processes that are the same across our medicines, shorten our timeline from initial concept to the first human dose, when compared to early development timelines for other drug modalities like small molecule and antibody medicines.

IONIS CLINICAL PIPELINE						
	MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
NEUROLOGICAL						
	Tofersen	SOD1-ALS	Biogen			
	Tominersen	Huntington's disease	Roche			
	IONIS-TTR-L _{Rx}	hATTR polyneuropathy	Ionis			
	IONIS-C9 _{Rx}	C9-ALS	Biogen			
	IONIS-MAPT _{Rx}	Alzheimer's disease	Biogen			
	ION859	Parkinson's disease	Biogen			
	IONIS-DNM2-2.5 _{Rx}	Centronuclear myopathy	Dynacure			
	ION464	Multiple system atrophy & Parkinson's disease	Biogen			
	ION541	ALS	Biogen			
CARDIOMETABOLIC						
	Pelacarsen	Lp(a) CVDRR ¹	Novartis			
	IONIS-TTR-L _{Rx}	ATTR cardiomyopathy	Ionis			
	IONIS-APOCIII-L _{Rx}	FCS	Ionis			
	IONIS-APOCIII-L _{Rx}	TG-driven diseases ²	Ionis			
	Vupanorsen	sHTG ³ /CVDRR	Pfizer			
	IONIS-FB-L _{Rx}	Nephropathy	Roche			
	IONIS-AGT-L _{Rx}	Treatment-resistant hypertension	Ionis			
	IONIS-FXI-L _{Rx}	Clotting disorders	Bayer			
	ION449	CVD	AstraZeneca			
	IONIS-GHR-L _{Rx}	Acromegaly	Ionis			
	IONIS-GCGR _{Rx}	Diabetes	Suzhou-Ribo			
	ION532	Kidney disease	AstraZeneca			
	ION839	NASH	AstraZeneca			
	ION224	NASH	Ionis			
OTHER						
INFECTIOUS						
	IONIS-HBV _{Rx}	Hepatitis B virus infection	GSK			
CANCER						
	IONIS-AR-2.5 _{Rx}	Prostate cancer	Suzhou-Ribo			
	Danvatirsen	Cancer	Ionis			
	ION736	Cancer	AstraZeneca			
	ION537	Cancer	MD Anderson			
	ION251	Multiple Myeloma	Ionis			
OPHTHALMOLOGY						
	IONIS-FB-L _{Rx}	AMD	Roche			
	ION357	Retinitis pigmentosa	ProQR			
PULMONOLOGY & ALLERGY						
	IONIS-ENAC-2.5 _{Rx}	Cystic fibrosis	Ionis			
	IONIS-ENAC-2.5 _{Rx}	COPD	Ionis			
	IONIS-PKK-L _{Rx}	Hereditary angioedema	Ionis			
HEMATOLOGY						
	IONIS-TMPRSS6-L _{Rx}	β-thalassemia	Ionis			
OTHER						
	ION253	GI Autoimmune disease	Janssen			

1. CVDRR: Cardiovascular disease risk reduction. 2. TG: Triglyceride. 3. sHTG: Severe hypertriglyceridemia.

The above table lists the medicines in our clinical pipeline. We categorize patient studies to establish a medicine's safety profile as Phase 1/2 and those studies in healthy volunteers as Phase 1. The table includes the disease indication, a partner (if the medicine is partnered), and the development status of each medicine. We have included descriptions for each of our medicines in Phase 2 and Phase 3 development below.

We are focused on pioneering new markets and changing standards of care creating a deep and broad pipeline of over 30 potentially first-in-class and/or best-in-class medicines in clinical trials. We believe we have the potential to deliver significant value to patients affected by the devastating diseases each medicine addresses, many of which have limited or no treatment options.

Our Phase 3 Medicines

As of February 2020, we have five medicines in six Phase 3 studies: tofersen, tominersen, IONIS-TTR-L_{Rx}, IONIS-APOCIII-L_{Rx}, and pelacarsen.

IONIS CLINICAL PIPELINE – PHASE 3					
MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
NEUROLOGICAL					
Tofersen	SOD1-ALS	Biogen			
Tominersen	Huntington's disease	Roche			
IONIS-TTR-L _{Rx}	hATTR polyneuropathy	Ionis			
CARDIOMETABOLIC					
IONIS-TTR-L _{Rx}	ATTR cardiomyopathy	Ionis			
IONIS-APOCIII-L _{Rx}	FCS	Ionis			
Pelacarsen	Lp(a) CVDRR	Novartis			

Tofersen (IONIS-SOD1_{Rx} or BIIB067) – Tofersen is an investigational antisense medicine we designed to inhibit the production of superoxide dismutase 1, or SOD1, which is a well understood genetic cause of familial amyotrophic lateral sclerosis, or ALS. SOD1-ALS is a rare, fatal, neurodegenerative disorder caused by a mutation in the *SOD1* gene leading to a progressive loss of motor neurons. As a result, people with SOD1-ALS experience increasing muscle weakness, loss of movement, difficulty breathing and swallowing and eventually succumb to the disease. Current treatment options for people with SOD1-ALS are extremely limited, with no medicines that significantly slow disease progression.

Our partner, Biogen, conducted a Phase 1/2 study that demonstrated proof of biology and proof of concept. At the highest dose tested, treatment with tofersen over a three month period resulted in a statistically significant lowering of SOD1 protein levels in the CSF and positive numerical trends across three efficacy endpoints: slowing of clinical decline as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised, or ALSFRS-R, slowing of decline in respiratory function as measured by vital capacity and slowing of decline in muscle strength as measured by a handheld device, all compared to placebo. The efficacy, safety and tolerability profile in this study supported the continued development of tofersen in ALS.

In December 2020, Biogen completed enrollment in the VALOR Phase 3 clinical study of tofersen. In the VALOR study Biogen is assessing the efficacy and safety of tofersen versus placebo in approximately 100 patients with SOD1-ALS. The primary endpoint of this study is an analysis based on the ALSFRS-R, which is a validated rating instrument that monitors the progression of disability in patients with ALS.

In December 2018, Biogen exercised its option to license tofersen based on the positive interim analysis from the Phase 1/2 study. As a result, Biogen is responsible for global development, regulatory and commercialization activities and costs for tofersen.

Tominersen (IONIS-HTT_{Rx} or RG6042) – Tominersen is an investigational antisense medicine we designed to target the underlying cause of Huntington's disease, or HD, by reducing the production of the toxic mutant huntingtin protein, or mHTT. HD is a rare, inherited, genetic brain disorder that results in the progressive deterioration of mental abilities and physical control. In the U.S. and major European markets there are approximately 80,000 individuals with symptomatic HD and more than five-fold this number with presymptomatic HD. HD is one of several genetic diseases in which the body mistakenly repeats certain DNA sequences, often referred to as triplet repeat disorders. The resulting mHTT protein is toxic and gradually damages neurons in the brain. Symptoms of HD usually appear between the ages of 30 to 50 years and continually worsen over a 10 to 25-year period. Ultimately, the weakened individual succumbs to pneumonia, heart failure or other complications. Presently, there are no disease-modifying treatments available for HD patients, with current medicines only managing some disease symptoms.

We completed a randomized, placebo-controlled, dose escalation, Phase 1/2 clinical study of tominersen in patients with early stage HD. In this study, we observed dose-dependent reductions of mHTT among patients treated with tominersen. Tominersen also demonstrated a favorable safety and tolerability profile in this Phase 1/2 clinical study. In March 2018, we reported data from the study that demonstrated substantial reductions in the mHTT as

observed in the cerebral spinal fluid, or CSF. The reductions in mHTT were in the target range that produced disease reversal in preclinical models of HD. Tominersen was the first medicine to demonstrate disease-modifying potential by lowering the root cause of HD, the mHTT protein. There were no serious adverse events reported and no participants discontinued from the study. The data from this study were published in *The New England Journal of Medicine* in May 2019.

Following the results from the Phase 1/2 study, Roche initiated the Phase 3 GENERATION HD1 study of tominersen and completed enrollment in April 2020. GENERATION HD1 is a randomized, multicenter, blinded, placebo-controlled study in approximately 800 patients with HD. The GENERATION HD1 study is evaluating the efficacy and safety of bi-monthly and tri-annual dosing regimens of tominersen for 25 months of dosing. The global primary endpoint is the change from baseline in the composite Unified Huntington Disease Rating Scale, or cUHDRS, and the U.S. primary endpoint is the change from baseline in the Total Functional Capacity, or TFC.

In addition to the Phase 3 study, all participants who took part in the Phase 1/2 study continued to receive tominersen as part of an OLE study to assess the safety and tolerability of tominersen. In parallel with the OLE, Roche initiated a natural history study in a similar patient population to the OLE. The natural history study is planned as a 15-month study aimed at further understanding the role of mHTT in disease progression and includes approximately 100 participants. There is no drug treatment in the natural history study, as the goal is to understand the natural progression of HD.

The European Medicines Agency, or EMA, granted PRiority MEDicines scheme, or PRIME, designation to tominersen. EMA PRIME status is granted to medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. The FDA and EMA granted Orphan Medicine Designation for tominersen to treat people with HD.

We entered into a collaboration with Roche to develop and commercialize antisense medicines to treat HD in April 2013. In December 2017, Roche exercised its option to license tominersen. As a result, Roche is responsible for global development, regulatory and commercialization activities and costs for tominersen.

IONIS-TTR-L_{Rx} – IONIS-TTR-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of transthyretin, the same protein inhibited by TEGSEDI (inotersen). There are two types of ATTR amyloidosis: hATTR amyloidosis and wt-ATTR amyloidosis. We are developing IONIS-TTR-L_{Rx} as a monthly self-administered subcutaneous injection for the treatment of people with all forms of TTR amyloidosis. See the TEGSEDI summary under “Our Marketed Medicines” section for more information about hATTR amyloidosis and wt-ATTR amyloidosis.

In September 2019, we reported results from the Phase 1 study with IONIS-TTR-L_{Rx} in healthy volunteers at the Heart Failure Society of America Annual Meeting. In this study, subjects treated with IONIS-TTR-L_{Rx} achieved dose-dependent reductions of TTR protein of up to 94 percent and IONIS-TTR-L_{Rx} demonstrated a favorable safety and tolerability profile, consistent with our other liver LICA medicines.

The first of two indications we are pursuing is for the treatment of patients with polyneuropathy caused by hATTR amyloidosis. We initiated the global NEURO-TTRansform Phase 3 study for IONIS-TTR-L_{Rx} in November 2019. NEURO-TTRansform is a multi-center, randomized, open-label study designed to evaluate the efficacy and safety of IONIS-TTR-L_{Rx} in up to 140 patients with polyneuropathy due to hATTR amyloidosis. The current study will be compared to the historical placebo arm from the TEGSEDI (inotersen) NEURO-TTR Phase 3 study that we completed in 2017. The NEURO-TTRansform study includes multiple primary endpoints, including the percent change from baseline in serum TTR concentration, modified Neuropathy Impairment Score +7 (mNIS+7), and in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN).

The second indication we are pursuing is for the treatment of patients with cardiomyopathy caused by hereditary or wild-type TTR amyloidosis. In January 2020, we initiated the global CARDIO-TTRansform Phase 3 cardiovascular outcome study. CARDIO-TTRansform is a randomized, blinded, placebo-controlled study in up to 750 patients with cardiomyopathy caused by hereditary or wt-TTR amyloidosis. The CARDIO-TTRansform study includes co-primary outcome measures of cardiovascular death and frequency of cardiovascular clinical events.

IONIS-APOCIII-L_{Rx} – IONIS-APOCIII-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of apoC-III for patients who are at risk of disease due to elevated triglyceride levels. ApoC-III is a protein produced in the liver that regulates triglyceride metabolism in the blood. People with severely elevated triglycerides,

such as people with FCS, are at high risk for acute pancreatitis and an increased risk of CVD. ApoC-III is also the target of WAYLIVRA (volanesorsen), the only medicine approved for the treatment of people with FCS. See the WAYLIVRA summary under “Our Marketed Medicines” section for more information about FCS.

We initiated a Phase 3 study in December 2020 in patients with FCS based on the Phase 2 data described below. We believe that the enhancements offered by our LICA technology can provide greater reductions in triglycerides, significantly lower doses and less frequent administration, compared to WAYLIVRA.

In January 2020, we reported positive results from a Phase 2 clinical study in patients with hypertriglyceridemia and at high risk of or with established CVD. Patients were treated with multiple doses of IONIS-APOCIII-L_{Rx} administered weekly, bi-weekly, or monthly. IONIS-APOCIII-L_{Rx} achieved statistically significant, dose-dependent reductions in fasting triglycerides compared to placebo at all dose levels. Additionally, at the highest monthly dose, 91 percent of patients achieved serum triglycerides of ≤ 150 mg/dL, the recognized threshold for cardiovascular risk, compared to less than 5 percent of patients in the placebo group. IONIS-APOCIII-L_{Rx} also achieved statistical significance in numerous key secondary endpoints, including significant reductions in apoC-III, very low-density lipoprotein cholesterol, or VLDL-C, and remnant cholesterol, and a statistically significant increase in high-density lipoprotein cholesterol, or HDL-C. IONIS-APOCIII-L_{Rx} demonstrated a favorable safety and tolerability profile in the study.

Pelacarsen (IONIS-APO(a)-L_{Rx} or TQJ230) – Pelacarsen is an investigational LICA antisense medicine designed to inhibit the production of apolipoprotein(a), or Apo(a), in the liver to offer a direct approach for reducing lipoprotein(a), or Lp(a). Elevated Lp(a) is recognized as an independent, genetic cause of CVD. Lp(a) levels are determined at birth and lifestyle modification, including diet and exercise, do not impact Lp(a) levels. It is estimated that there are more than eight million people living with CVD and elevated levels of Lp(a). Inhibiting the production of Apo(a) in the liver reduces the level of Lp(a) in blood, potentially slowing down or reversing cardiovascular disease in people with hyperlipoproteinemia(a), a condition in which individuals have levels of Lp(a) greater than 50 mg/dL, the recognized threshold for risk of CVD.

We believe antisense technology is well suited to address hyperlipoproteinemia(a) because antisense technology specifically targets the RNA that codes for all forms of the Apo(a) molecule. Furthermore, we believe addressing elevated Lp(a) is the next important horizon in CVD risk reduction.

In December 2019, Novartis initiated the Phase 3 Lp(a)HORIZON study of pelacarsen, a global, randomized, blinded, placebo-controlled outcomes study in approximately 7,500 patients with elevated Lp(a) levels and a prior cardiovascular event, based on the Phase 2 data described below. Patients will be treated with 80 mg of pelacarsen administered monthly by subcutaneous injection. The primary endpoint in Lp(a)HORIZON is the time to occurrence of first major adverse cardiovascular event, or MACE.

We reported results of the Phase 2 study with pelacarsen in patients with hyperlipoproteinemia(a) at the American Heart Association, or AHA, annual meeting in November 2018. In this clinical study, we observed statistically significant and dose dependent reductions from baseline in Lp(a) levels. Approximately 98 percent of patients who received the highest dose in the study demonstrated a reduction in Lp(a) levels to below 50 mg/dL. This study of pelacarsen was the longest and largest clinical study in patients with established CVD and elevated levels of Lp(a). At the time, this study was also the longest and largest clinical study of any of our LICA medicines. Pelacarsen demonstrated a favorable safety and tolerability profile in the study. Compliance in the treatment arm of the study was almost 90 percent, which was higher than what we observed in the placebo group.

We initiated a collaboration with Novartis in January 2017 to advance pelacarsen. In February 2019, Novartis exercised its option to license pelacarsen. As a result, Novartis is responsible for global development, regulatory and commercialization activities and costs for pelacarsen.

Neurological Disease Medicines in Development

We are discovering and developing antisense medicines to treat people with neurological diseases. Our neurological medicines address a broad range of diseases in major regions of the brain and all central nervous system, or CNS, cell types. Our antisense medicines aim to address both large and rare patient populations. We are currently investigating potential disease-modifying treatments for common neurological diseases including, Alzheimer’s disease and Parkinson’s disease. We also have multiple investigational medicines in clinical trials for

rare neurological diseases, including ALS and hATTR polyneuropathy. According to the National Institute of Neurological Disorders and Stroke, or NINDS, at the National Institutes of Health, or NIH, a third of the 7,000 known rare diseases are neurological disorders or thought to include a neurological component.

IONIS' Neurological Disease Clinical Pipeline

IONIS CLINICAL PIPELINE – NEUROLOGICAL						
	MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
NEUROLOGICAL	IONIS-TTR-L _{Rx}	hATTR polyneuropathy	Ionis			
	Tofersen	SOD1-ALS	Biogen			
	Tominersen	Huntington's disease	Roche			
	IONIS-C9 _{Rx}	C9-ALS	Biogen			
	IONIS-MAPT _{Rx}	Alzheimer's disease	Biogen			
	ION859	Parkinson's disease	Biogen			
	ION464	Multiple system atrophy & Parkinson's disease	Biogen			
	ION541	ALS	Biogen			
	IONIS-DNM2-2.5 _{Rx}	Centronuclear myopathy	Dynacure			

Wholly Owned Medicines

IONIS-TTR-L_{Rx} – See the medicine description under “Our Phase 3 Medicines” section above.

Partnered Medicines

Tofersen – See the medicine description under “Our Phase 3 Medicines” section above.

Tominersen – See the medicine description under “Our Phase 3 Medicines” section above.

IONIS-C9_{Rx} (BIIB078) – IONIS-C9_{Rx} is an investigational antisense medicine we designed to selectively inhibit the production of the mutated chromosome 9 open reading frame 72, or *C9ORF72*, gene. A mutation in this gene results in an inherited form of ALS, referred to as C9ORF72-ALS, or C9-ALS, the most prevalent genetic cause of ALS worldwide. This mutation can lead to rapid progressive loss of motor neurons and is a fatal disease characterized by muscle weakness, loss of movement, and difficulty breathing and swallowing.

We and Biogen are collaborating to develop IONIS-C9_{Rx} to treat patients with this genetic form of ALS. In August 2018, Biogen initiated a Phase 1/2 clinical study evaluating IONIS-C9_{Rx} in adult patients with C9ORF72-ALS. The current study is a randomized, blinded, placebo-controlled study designed to assess the safety, tolerability, and pharmacokinetics of multiple ascending doses of IONIS-C9_{Rx} administered intrathecally. IONIS-C9_{Rx} is the second medicine from our Biogen collaboration targeting a genetic form of ALS. The first is tofersen, our medicine we designed to treat SOD1 related ALS, caused by a mutation in the *SOD1* gene.

IONIS-MAPT_{Rx} (BIIB080) – IONIS-MAPT_{Rx} is an investigational antisense medicine we designed to selectively inhibit production of the microtubule-associated protein tau, or tau, protein in the brain. We are collaborating with Biogen to develop IONIS-MAPT_{Rx} to treat people with Alzheimer's disease, or AD, and potentially other neurodegenerative disorders characterized by the deposition of abnormal tau protein in the brain, such as certain forms of frontotemporal degeneration, or FTD, and progressive supranuclear palsy, or PSP.

The tau protein is a contributor or cause of certain neurodegenerative diseases, known as tauopathies, characterized by the deposition of abnormal tau protein in neurons in the brain. AD and FTD are characterized predominantly by memory impairment and behavioral changes, resulting in a person's inability to independently perform daily activities. PSP is characterized by problems with walking and control of movement, sleep disorder and loss of memory and ability to reason. AD generally occurs late in life and may progress to death in five to 20 years after the onset of the disease. FTD and PSP have a more rapid disease progression. In the U.S., there are approximately five million people living with AD, approximately 55,000 people living with FTD and approximately 20,000 people living with PSP.

We and Biogen completed a blinded, randomized, placebo-controlled, dose-escalation Phase 1/2 study of IONIS-MAPT_{Rx} to evaluate the safety and activity of once-monthly intrathecal injections of IONIS-MAPT_{Rx} in patients with mild AD. In February 2021, Biogen reported data from this Phase 1/2 study that IONIS-MAPT_{Rx} was generally well tolerated and demonstrated dose and time-dependent target reductions. Biogen plans to advance IONIS-MAPT_{Rx} into a Phase 2 clinical trial in patients with Alzheimer's disease.

In December 2019, Biogen exercised its option to license IONIS-MAPT_{Rx}. We are responsible for completing the Phase 1/2 in study patients with mild AD and a one-year long-term extension study. Biogen will have responsibility for global development, regulatory and commercialization activities and costs for IONIS-MAPT_{Rx}.

ION859 (BIIB094) – ION859 is an investigational antisense medicine we designed to inhibit the production of the Leucine Rich Repeat Kinase 2, or LRRK2, protein as a potential therapy for Parkinson’s disease, or PD. The most common genetic mutations in PD are found in the LRRK2 protein. It is believed that increased LRRK2 protein activity could be one of the key drivers for developing PD.

PD is a progressive neurodegenerative disease characterized by loss of neurons in the motor system. Patient’s with PD can experience tremors, loss of balance and coordination, stiffness, slowing of movement, changes in speech and in some cases cognitive decline. PD is ultimately fatal. There are treatments that can relieve symptoms, but there is no disease modifying therapy.

We and Biogen are collaborating to develop ION859 to treat patients with PD. In August 2019, Biogen initiated a Phase 1/2 clinical study evaluating ION859 in adult patients with PD. The current study is a randomized, blinded, placebo-controlled study designed to assess the safety, tolerability and pharmacokinetics of multiple ascending doses of ION859 administered intrathecally.

ION464 (BIIB101) – ION464 is an investigational antisense medicine we designed to inhibit the production of the alpha-synuclein protein as a potential therapy for PD, Multiple System Atrophy, or MSA, and related synucleinopathies. Alpha-synuclein protein abnormally accumulates in the brains of PD and MSA patients and is thought to be one of the key drivers of these diseases. It is believed that decreasing the production of the alpha-synuclein protein will reduce the toxic effects of gain-of-function mutations as well as the primary pathology in PD and MSA patients without alpha-synuclein mutations.

We and Biogen are collaborating to develop ION464 to treat patients with PD and MSA. In July 2020, Biogen initiated a Phase 1/2 clinical study evaluating ION464 in patients with MSA. The current study is a randomized, blinded, placebo-controlled study designed to assess the safety and tolerability of multiple doses of ION464 administered intrathecally.

ION541 (BIIB105) – ION541 is an investigational antisense medicine we designed to selectively inhibit the production of the ataxin-2, or ATXN2, protein. In approximately 90% of the ALS population, aggregates of the TDP-43 protein induce toxicity in motor neurons. ATXN2 has been shown to modulate TDP-43 toxicity and it is believed that reduction of ATXN2 will decrease the TDP-43 aggregates and reverse or prevent disease progression, providing therapeutic benefit to most ALS patients.

We and Biogen are collaborating to develop ION541 to treat patients with most forms of ALS, regardless of family history. In October 2020, Biogen initiated a Phase 1/2 clinical study evaluating ION541 in this broad ALS population. The current study is a randomized, blinded, placebo-controlled study designed to assess the safety, tolerability, and pharmacokinetics of multiple ascending doses of ION541 administered intrathecally. ION541 is the first medicine from our Biogen collaboration targeting all forms of ALS.

IONIS-DNM2-2.5_{Rx} (DYN101) – IONIS-DNM2-2.5_{Rx} is an investigational antisense medicine we designed to inhibit the production of Dynamin 2, or DNM2, protein for the treatment of centronuclear myopathy, or CNM. CNM is a group of rare, potentially fatal disorders of the skeletal muscle cells. It is characterized by muscle weakness, decreased muscle tone and muscle atrophy, ranging from severe to mild, and potentially life-threatening.

DNM2 reduction demonstrated improved muscle mass and muscle force, and extended lifespan in animal models of the most severe form of CNM.

We and Dynacure are collaborating to develop IONIS-DNM2-2.5_{Rx} to treat patients with CNM. In November 2019, Dynacure initiated a Phase 1/2 clinical study evaluating IONIS-DNM2-2.5_{Rx} in patients with CNM. The current study is an open-label study designed to assess the safety and tolerability of multiple doses of IONIS-DNM2-2.5_{Rx} administered intravenously.

Cardiometabolic Disease Medicines in Development

Developing medicines targeting CVD and metabolic disorders are important areas of focus for us. According to the World Health Organization, or WHO, CVD remains the number one cause of death globally. An estimated 17.9 million people died from CVD in 2016, representing approximately 30 percent of all deaths globally.

Our cardiovascular medicines target the major risk factors of cardiovascular disease, including cholesterol, triglycerides and hypertension. Metabolic disorders, such as nonalcoholic steatohepatitis, or NASH, are chronic diseases that affect tens of millions of people. There is a significant need for new therapies for these people. According to the American Liver Foundation, nonalcoholic fatty liver disease, or NAFLD, is the most common chronic liver condition in the U.S. It is estimated that about 25 percent of adults in the U.S. have NAFLD. Of those with NAFLD, about 20 percent have NASH or about 5% of adults in the U.S.

IONIS' Cardiometabolic Disease Clinical Pipeline

IONIS CLINICAL PIPELINE – CARDIOMETABOLIC						
	MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
CARDIOMETABOLIC	IONIS-TTR-L _{Rx}	ATTR cardiomyopathy	Ionis			
	IONIS-APOCIII-L _{Rx}	FCS	Ionis			
	IONIS-APOCIII-L _{Rx}	TG-driven diseases	Ionis			
	IONIS-AGT-L _{Rx}	Treatment-resistant hypertension	Ionis			
	IONIS-GHR-L _{Rx}	Acromegaly	Ionis			
	Pelacarsen	Lp(a) CVDRR	Novartis			
	Vupanorsen	sHTG/CVDRR	Pfizer			
	IONIS-FXI-L _{Rx}	Clotting disorders	Bayer			
	ION449	CVD	AstraZeneca			
	IONIS-GGCR _{Rx}	Diabetes	Suzhou-Ribo			

Wholly Owned Medicines

IONIS-TTR-L_{Rx} – See the medicine description under “Our Phase 3 Medicines” section above.

IONIS-APOCIII-L_{Rx} – See the medicine description under “Our Phase 3 Medicines” section above.

IONIS-AGT-L_{Rx} – IONIS-AGT-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of angiotensinogen to decrease blood pressure in people with treatment resistant hypertension, or TRH. Despite the availability of antihypertensive agents, TRH is still a major contributor to cardiovascular and renal disease.

Approximately 140 million adults globally and approximately 10 million adults in the U.S. have resistant hypertension, defined as failure to achieve a blood pressure goal of 140/90 (systolic/diastolic) despite the use of three or more antihypertensive medications. People with TRH have been found to have a three-fold higher chance of having fatal and non-fatal cardiovascular events relative to those with controlled hypertension.

We evaluated IONIS-AGT-L_{Rx} in two Phase 2 studies. The first study was in people with mild hypertension and the second was in people with TRH who were currently on two or three antihypertensive medications, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). Each study was randomized, blinded, placebo-controlled and designed to evaluate the safety and tolerability of IONIS-AGT-L_{Rx}.

In January 2021, we initiated the Phase 2b clinical study of IONIS-AGT-L_{Rx}, a randomized, blinded, placebo-controlled study in approximately 150 patients with TRH or uncontrolled hypertension who are currently on three or more antihypertensive medications, including ACE inhibitors or ARBs. The study is designed to evaluate multiple weekly doses administered subcutaneously. The primary endpoint is the change in systolic blood pressure (SBP) from baseline. The study will also assess numerous secondary endpoints, and safety and tolerability of IONIS-AGT-L_{Rx}.

IONIS-GHR-L_{Rx} – IONIS-GHR-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of the growth hormone receptor, or GHr, to decrease the circulating level of insulin-like growth factor-1, or IGF-1. IGF-1 is a hormone primarily produced in the liver that plays an important role in childhood growth. Several different diseases result from abnormally low or high levels of IGF-1, or an inappropriate response to this hormone. Elevated levels of IGF-1 results in acromegaly, a chronic, slowly progressing and potentially fatal disease. Because IGF-1 mediates the majority of the growth-promoting action of GH, reducing GHr production could in turn decrease levels of IGF-1 and provide a potential treatment for patients with acromegaly.

High levels of circulating GH and IGF-1 lead to multiple diseases characterized by organ overgrowth and physical disfigurement, such as enlarged hands, feet, and facial features. Patients with acromegaly also experience multiple chronic conditions, such as type 2 diabetes, hypertension, and respiratory complications, as well as premature death. Current treatments to block IGF-1 are often unsuccessful. Drug treatments to normalize IGF-1 levels are also available but are associated with potentially serious side effects.

We completed a Phase 1, blinded, placebo-controlled, dose-escalation study of IONIS-GHR-L_{Rx} in healthy volunteers. In this study, IONIS-GHR-L_{Rx} demonstrated a favorable safety and tolerability profile.

In November 2018, we initiated the Phase 2 proof of concept clinical study of IONIS-GHR-L_{Rx} in patients with acromegaly. The study is a randomized, blinded, placebo-controlled, multi-center study in acromegaly patients uncontrolled on select long-acting somatostatin receptor ligands.

In January 2021, we initiated a Phase 2 open label study evaluating IONIS-GHR-L_{Rx} as a monotherapy in patients with acromegaly. The open label study is designed to assess the clinical efficacy, safety and tolerability of IONIS-GHR-L_{Rx} of multiple doses administered monthly subcutaneously.

Partnered Medicines

Pelacarsen – See the medicine description under “Our Phase 3 Medicines” section above.

Vupanorsen – Vupanorsen is an investigational LICA medicine we designed to inhibit the production of the angiopoietin-like 3, or ANGPTL3, protein. People with elevated levels of the ANGPTL3 protein have high LDL-C and triglyceride levels. Studies show people with elevated levels of ANGPTL3 protein have an increased risk of premature heart attacks, increased arterial wall thickness and multiple metabolic disorders such as diseases resulting from increased liver fat. In contrast, people with lower levels of ANGPTL3 have lower LDL-C and triglyceride levels, and thus lower risk of heart attacks, lower prevalence of fatty liver and lower incidence of metabolic disorders.

In preclinical studies, treatment with an antisense medicine designed to inhibit the production of the ANGPTL3 protein in the liver resulted in lower liver fat accumulation and lower blood levels of LDL-C, triglycerides and very low-density lipoprotein cholesterol, or VLDL-C.

Results from a Phase 1/2 study of vupanorsen in healthy volunteers with elevated triglycerides were published in *The New England Journal of Medicine*. In the study, we observed that the people with elevated triglycerides achieved dose-dependent, statistically significant mean reductions in ANGPTL3 of up to 83 percent. Treatment with vupanorsen was also associated with statistically significant mean reductions in triglycerides of up to 66 percent, in LDL-C of up to 35 percent and in total cholesterol of up to 36 percent. In this study, vupanorsen demonstrated a favorable safety and tolerability profile.

In November 2020, Pfizer initiated the Phase 2b TRANSLATE-TIMI 70 clinical study of vupanorsen, a randomized, blinded, placebo-controlled study in approximately 260 patients with elevated non-HDL-C and triglycerides who are receiving a stable dose of a statin, based on the Phase 2 study described below. The study is designed to evaluate multiple doses and dose regimens versus placebo. The primary endpoint is percent change from baseline in non-HDL-C. The study will also assess the efficacy, safety, tolerability and pharmacokinetics of vupanorsen.

In January 2020, we reported positive results from a Phase 2 clinical study in patients with elevated levels of triglycerides, or hypertriglyceridemia, type 2 diabetes and NAFLD. Patients were treated with multiple doses of vupanorsen administered weekly and monthly. Vupanorsen achieved statistically significant, dose-dependent reductions in the study’s primary endpoint of fasting triglycerides compared to placebo at all dose levels. Vupanorsen also achieved statistical significance in multiple secondary endpoints, including dose-dependent reductions in ANGPTL3, apoC-III, very low-density lipoprotein (VLDL-C), non-HDL cholesterol and total cholesterol compared to placebo. Vupanorsen demonstrated a favorable safety and tolerability profile in the study.

In October 2019, we exclusively licensed vupanorsen to Pfizer. As a result, Pfizer is responsible for global development, regulatory and commercialization activities and costs beyond those associated with the above Phase 2 study. We have the option prior to regulatory filing for marketing approval, to participate in certain commercialization activities in the future with Pfizer in the U.S. and certain additional markets on pre-defined terms and based on meeting pre-defined criteria.

IONIS-FXI-L_{Rx} – IONIS-FXI-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of Factor XI. Factor XI is a clotting factor produced in the liver that is important in the growth of blood clots. High levels of Factor XI increase the risk of thrombosis. Thrombosis, characterized by the formation of a blood clot inside blood vessels, can cause heart attacks and strokes. People who are deficient in Factor XI have a lower incidence of thromboembolic events with minimal increase in bleeding risk. Although currently available anticoagulants reduce

the risk of thrombosis, physicians associate these anticoagulants with increased bleeding, which can be fatal. By inhibiting Factor XI production, we believe that IONIS-FXI-L_{Rx} can be used broadly as an anti-thrombotic in many different therapeutic settings for which additional safe and well tolerated anti-thrombotic medicines are needed.

In November 2016, we completed a Phase 2 blinded, randomized, placebo-controlled study of the parent medicine, IONIS-FXI_{Rx}, in people with end-stage renal disease, or ESRD, on hemodialysis. In this Phase 2 study, patients treated with IONIS-FXI_{Rx} achieved statistically significant, dose-dependent reductions in Factor XI activity. In this study, IONIS-FXI_{Rx} demonstrated a favorable safety and tolerability profile. There were no treatment-related major or clinically relevant non-major bleeding events.

We conducted a Phase 1, blinded, randomized, placebo-controlled, dose-escalation study of IONIS-FXI-L_{Rx} in healthy volunteers. In this study, IONIS-FXI-L_{Rx} produced significant reductions in FXI activity and FXI antigen, without evidence of increased bleeding. Additionally, IONIS-FXI-L_{Rx} demonstrated a favorable safety and tolerability profile in this study. We and Bayer are planning to report the data from this Phase 1 study this year.

In February 2017, we licensed IONIS-FXI-L_{Rx} to Bayer. As a result, Bayer is responsible for global development, regulatory and commercialization activities and costs.

In August 2020, Bayer initiated the Phase 2b RE-THINc clinical study of IONIS-FXI-L_{Rx}, a randomized, blinded, placebo-controlled study in approximately 290 patients with ESRD on hemodialysis. The study is designed to evaluate multiple monthly doses administered subcutaneously. The primary endpoint is incidence of major bleeding and clinically relevant non-major bleeding. The study will also assess numerous secondary endpoints, and safety and tolerability of IONIS-FXI-L_{Rx}.

ION449 – ION449 (IONIS-AZ4-2.5-L_{Rx}) is an investigational LICA medicine we designed to reduce the production of proprotein convertase subtilisin/kexin type 9, or PCSK9, in the liver. PCSK9 is integrally involved in the regulation of LDL-cholesterol. Genetic studies have shown that individuals with life-long reductions of LDL-C due to reduced function of PCSK9 have substantially reduced risk of CVD.

In October 2020, we reported positive results from a Phase 1 clinical study of ION449 in healthy volunteers. Participants were treated with single subcutaneous doses and ION449 demonstrated dose-dependent mean reductions in circulating plasma PCSK9 and LDL-C levels of greater than 90% and up to 70%, respectively.

In November 2020, AstraZeneca initiated the Phase 2b randomized, blinded placebo-controlled clinical study that will enroll approximately 110 patients with LDL-C levels between 70 and 190mg/dl and receiving statin therapy. The study is designed to evaluate multiple monthly subcutaneous doses versus placebo. The study will also assess safety and tolerability, and multiple secondary endpoints.

IONIS-GCGR_{Rx} – IONIS-GCGR_{Rx} is an investigational antisense medicine designed to inhibit the production of the glucagon receptor, or GCGR, to treat patients with type 2 diabetes. GCGR is a receptor for the hormone glucagon. Glucagon is a hormone that opposes the action of insulin and stimulates the liver to produce glucose, particularly in type 2 diabetes. In patients with advanced diabetes, uncontrolled glucagon action can lead to significant increase in blood glucose level. In addition, reducing GCGR produces more active glucagon-like peptide, or GLP-1, a hormone that preserves pancreatic function and enhances insulin secretion.

Diabetes is a chronic disease in which the blood glucose levels are too high. Although glucose is an important source of energy for your body and is vital to your health, uncontrolled increases in glucose can lead to serious health problems, such as diabetes. Diabetes is separated into type 1 and type 2. In type 1 diabetes, the body does not make insulin. In type 2 diabetes, the more common type, the body does not respond properly to insulin and, therefore, blood glucose levels are not adequately controlled.

We and Suzhou-Ribo are collaborating to develop IONIS-GCGR_{Rx} to treat patients with type 2 diabetes. In October 2019, Suzhou-Ribo initiated a Phase 2 clinical study evaluating IONIS-GCGR_{Rx} in patients with type 2 diabetes.

Other Medicines in Development

We continue to advance medicines in clinical development that are outside of our core franchises, such as medicines targeting pulmonary diseases, cancer and infectious diseases.

IONIS' Other Medicines in Clinical Pipeline

IONIS CLINICAL PIPELINE – OTHER						
	MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
WHOLLY OWNED						
	IONIS-ENAC-2.5 _{Rx}	Cystic fibrosis	Ionis			
	IONIS-ENAC-2.5 _{Rx}	COPD	Ionis			
	IONIS-PKK-L _{Rx}	Hereditary angioedema	Ionis			
	Danvatirsen	Cancer	Ionis			
	IONIS-TMPRSS6-L _{Rx}	β-thalassemia	Ionis			
PARTNERED						
	IONIS-HBV _{Rx}	Hepatitis B virus infection	GSK			
	IONIS-AR-2.5 _{Rx}	Prostate cancer	Suzhou-Ribo			
	IONIS-FB-L _{Rx}	AMD	Roche			
	IONIS-FB-L _{Rx}	IgA Nephropathy	Roche			
	ION357	Retinitis pigmentosa	ProQR			

Wholly Owned Medicines

IONIS-ENAC-2.5_{Rx} – IONIS-ENAC-2.5_{Rx} is an investigational antisense medicine we designed to selectively reduce epithelial sodium channel, or ENaC, to treat people with cystic fibrosis, or CF, and chronic obstructive pulmonary disease, or COPD. CF is an autosomal recessive disorder caused by mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator, or CFTR. CFTR is a chloride channel expressed in epithelial cells, including those in the lung. Targeting ENaC may enable treatment of all forms of CF regardless of CFTR mutations, unlike existing therapeutics. CF is a multisystem disease that mostly affects the lungs, clogging airways due to mucus build-up and resulting in inflammation and infection. This disease is characterized by a progressive decline in lung function with acute periods of worsened symptoms, known as pulmonary exacerbations. Despite progress with other treatments, there remains a need for additional effective treatment options.

In preclinical studies in mouse models of CF, treatment with ENaC-targeting antisense medicines specifically suppressed ENaC expression, resulting in the reduction of markers of CF mucus pathology and improved lung function. Treatment not only prevented manifestations of the disease from occurring but also reversed existing manifestations of disease in the animal model.

In December 2018, we initiated a Phase 1/2 blinded, placebo-controlled, dose-escalation study to evaluate the safety and efficacy of IONIS-ENAC-2.5_{Rx} delivered directly to the lung via a nebulizer. The study consisted of three parts: a single ascending dose, or SAD, regimen and a multiple ascending dose, or MAD, regimen in healthy volunteers, followed by a MAD regimen in patients with CF.

In October 2020, we reported positive results from the healthy volunteer portions of the Phase 1/2 study. IONIS-ENAC-2.5_{Rx} demonstrated a significant decrease in the expression of ENaC with a favorable safety and tolerability profile, representing proof-of-concept for pulmonary delivery of an antisense medicine directly to the lung. In November 2020, we completed enrollment in the MAD portion in patients with CF.

COPD is a progressive and chronic inflammatory lung disease that causes obstructed airflow in the lungs and is the third leading cause of death globally. It is estimated to affect approximately 16 million people in the U.S. Targeting ENaC is believed to increase airway surface hydration and improve lung clearance.

In a preclinical mouse model of woodsmoke, treatment with an ENaC-targeting antisense medicine through aerosol delivery resulted in broad distribution in the lung and improved lung function.

In December 2020, we initiated a Phase 1/2 study in patients with COPD with chronic bronchitis. The current study is a blinded, placebo-controlled, single dose study to evaluate the safety and efficacy of IONIS-ENAC-2.5_{Rx} delivered directly to the lung via a nebulizer.

IONIS-PKK-L_{Rx} – IONIS-PKK-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of prekallikrein, or PKK, to treat people with hereditary angioedema, or HAE. It is a rare genetic disease that is characterized by rapid and painful attacks of inflammation in the hands, feet, limbs, face, abdomen, larynx and trachea and can be fatal if swelling occurs in the larynx. PKK plays an important role in the activation of inflammatory mediators associated with acute attacks of HAE. By inhibiting the production of PKK, IONIS-PKK-L_{Rx} could be an effective prophylactic approach to preventing or reducing the severity of HAE attacks.

In August 2019, we initiated a Phase 2 study evaluating IONIS-PKK-L_{Rx} in patients with HAE. The current study is a randomized, blinded, placebo-controlled study designed to assess the clinical efficacy, safety and tolerability of IONIS-PKK-L_{Rx} administered subcutaneously.

Results from the Phase 1 study in healthy volunteers and a compassionate-use study of IONIS-PKK_{Rx} and IONIS-PKK-L_{Rx} in patients living with severe bradykinin-mediated angioedema were published in September 2020 in *The New England Journal of Medicine*. In the study, we observed that the medicines reduced plasma prekallikrein activity levels and showed evidence of clinical efficacy in reducing the number of breakthrough attacks per month in patients over the course of the treatment, including complete resolution in a patient with Type 1 HAE, the most common form of the disease.

Danvatirsén – Danvatirsén (formerly IONIS-STAT3-2.5_{Rx}) is an investigational antisense medicine we designed to inhibit the production of signal transducer and activator of transcription 3, or STAT3, to treat people with cancer. STAT3 is a protein involved in the translation of key factors critical for tumor cell growth and survival. STAT3 is over-active in a variety of cancers, including brain, lung, breast, bone, liver and multiple myeloma. Overactivity in STAT3 prevents cancer cell death and promotes tumor cell growth.

In October 2018, we announced data from a Phase 1/2 study of danvatirsén in combination with durvalumab in recurrent metastatic head and neck cancer. The combination treatment resulted in seven percent of patients achieving a complete tumor response and 23 percent achieving either a partial or complete tumor response. This response rate is estimated to be double that with durvalumab alone, based on previous studies in this difficult to treat patient population. Results from this study demonstrated a safety and tolerability profile supportive of continued development.

IONIS-TMPRSS6-L_{Rx} – IONIS-TMPRSS6-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of transmembrane protease, serine 6, or TMPRSS6, to treat anemia and iron toxicity in people with β -thalassemia, a disease caused by mutations in the *beta globin* gene. TMPRSS6 is a protein produced in the liver that is important in the regulation of the body's iron homeostasis through the control of the iron regulatory protein hepcidin. Inhibition of TMPRSS6 leads to increased production of hepcidin, which results in more effective red blood cell production in the bone marrow and reduced iron toxicity in multiple organs, including the liver as a result of improved control of iron availability.

Patients with β -thalassemia can experience severe anemia, marrow expansion, bone deformities, as well as iron toxicity. While the severity of anemia varies between patients, iron toxicity is a common complication leading to high rates of mortality as a result of iron accumulation in major organs, such as the heart and liver. The current standard of care is managing patients' symptoms with blood transfusions, and iron chelation medicines designed to remove extra iron from blood.

β -thalassemia can be further subdivided into patients with transfusion-dependent thalassemia, or TDT, and non-transfusion dependent thalassemia, or NDT, including β -thalassemia intermedia. Although transfusions are not needed to support life in patients with NDT, the associated complications of the disease are severe and often fatal.

Results from preclinical and clinical studies suggest that reducing levels of TMPRSS6 may be an effective strategy to control iron availability, reduce liver iron toxicity and increase red blood cell production under conditions of β -thalassemia. In a randomized, blinded, placebo-controlled, dose-escalation Phase 1 study in healthy volunteers, we demonstrated dose-dependent reductions of serum iron and serum transferrin saturation. Additionally, we observed an increase in serum hepcidin and predicted changes in hemoglobin. IONIS-TMPRSS6-L_{Rx} demonstrated a favorable safety and tolerability profile. In December 2018, we presented positive Phase 1 data at the American Society of Hematology Annual Meeting.

In August 2020, we initiated a Phase 2a open label study evaluating IONIS-TMPRSS6-L_{Rx} in patients with NDT β -thalassemia intermedia. The open label study is designed to assess the clinical efficacy, safety and tolerability of IONIS-TMPRSS6-L_{Rx} administered monthly subcutaneously.

Partnered Medicines

IONIS-HBV_{Rx} – IONIS-HBV_{Rx} is an investigational antisense medicine we designed to inhibit the production of viral proteins associated with hepatitis B virus, or HBV. These include proteins associated with infection and replication, including the hepatitis B surface antigen, or HBsAg, which is present in both acute and chronic infections and is associated with a poor prognosis in people with chronic HBV infection.

HBV infection is a serious health problem that can lead to significant and potentially fatal health conditions, including cirrhosis, liver failure and liver cancer. Chronic HBV infection is one of the most common persistent viral infections in the world. Currently available therapies, although effective in reducing circulating HBV in the blood, do not effectively inhibit HBV antigen production and secretion, which are associated with poor prognosis and increased risk of liver cancer.

GSK reported results of the Phase 2 study with IONIS-HBV_{Rx} in patients with chronic hepatitis B virus infection at the American Association for the Study of Liver Diseases annual meeting in November 2019. In the Phase 2 study with IONIS-HBV_{Rx}, the medicine demonstrated target engagement with dose dependent declines in HBsAg with up to 3-log reductions in HBsAg at one month, including two patients who achieved reductions in HBsAg and HBV DNA below levels of detection. Additionally, IONIS-HBV_{Rx} demonstrated a favorable safety and tolerability profile.

In August 2019, GSK exercised its option to license our HBV program following the positive Phase 2 results described above. As a result, GSK is responsible for global development, regulatory and commercialization activities and costs for the HBV program.

In August 2020, GSK launched a broad Phase 2 program and initiated the Phase 2b B-Clear clinical study of IONIS-HBV_{Rx} in patients with chronic hepatitis B virus. The Phase 2b B-Clear study is a randomized, blinded, placebo-controlled study in approximately 440 patients with chronic hepatitis B virus infection. The primary endpoint is the percentage of patients achieving HBV surface antigen and HBV DNA less than the lower limit of quantitation. The study will also assess multiple secondary endpoints and the safety and tolerability of IONIS-HBV_{Rx}.

In the fourth quarter of 2020, GSK initiated two open label Phase 2 studies, B-Fine and B-Together, in patients with chronic hepatitis B virus. The B-Fine clinical study of IONIS-HBV_{Rx} is designed to investigate the hepatitis B virus surface antigen and assess liver biopsy samples for phenotyping. The B-Together study is designed to investigate if treatment of IONIS-HBV_{Rx} followed by pegylated interferon treatment can increase the rate of hepatitis B virus surface antigen loss in patients on stable nucleoside analogue therapy.

IONIS-AR-2.5_{Rx} – IONIS-AR-2.5_{Rx} is an investigational antisense medicine we designed to treat people with prostate cancer by reducing the production of all known forms of androgen receptor, or AR, including variants of the AR gene. Prostate cancer is the second leading cause of cancer deaths in American men. Prostate cancer growth, proliferation and progression are all androgen-dependent and AR function is involved in disease progression at all stages of prostate cancer. For patients diagnosed with metastatic prostate cancer, current treatments largely involve opposing the action of androgens by blocking the androgen receptor or removing circulating androgens. Resistance to current therapies is frequent and can occur through a variety of mechanisms including the activation of AR signaling in tumor cells through the amplification, overexpression and mutation of the AR gene.

An open-label, dose-escalation, Phase 1/2 clinical study of IONIS-AR-2.5_{Rx} was completed in people with advanced tumors for which the androgen receptor pathway is potentially a contributing factor. The study was primarily conducted in prostate cancer patients and it showed durable responses in a number of those patients. Results from this study demonstrated a safety and tolerability profile supportive of continued development.

In March 2017, we licensed IONIS-AR-2.5_{Rx} to Suzhou-Ribo to develop and commercialize the medicine in China.

IONIS-FB-L_{Rx} – IONIS-FB-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of complement factor B, or FB. FB is produced predominantly in the liver and circulates at high levels throughout the vascular system where it plays a pivotal role in an innate immunogenic cascade. Genetic association studies have shown that overactivity of this cascade has been associated with the development of several complement-mediated diseases, including dry age-related macular degeneration, or AMD, and IgA nephropathy, or IgAN.

AMD is the leading cause of central vision loss in developed countries. It is estimated that the disease will affect more than three million people in the U.S. by 2026. AMD is believed to be a systemic disease with local disease manifestation at the aging retinal macula. AMD gradually destroys vision in the center of the visual field due to progressive damage of the retina. Geographic atrophy, or GA, is an advanced form of AMD and accounts for approximately fifteen percent of all AMD.

IgAN is one of the most common causes of inflammation that impairs the filtering ability of kidneys and is an important cause of chronic kidney disease and renal failure. Also known as Berger's disease, IgAN is characterized by deposits of IgA in the kidneys, resulting in inflammation and tissue damage. The clinical presentation, disease progression and histologic findings are highly variable.

In May 2017, we reported data from a randomized, placebo-controlled, dose-escalation Phase 1 study evaluating IONIS-FB-L_{Rx} in 54 healthy volunteers. Subjects treated with a single dose of IONIS-FB-L_{Rx} achieved dose-dependent reductions in plasma FB of up to 50 percent. Treatment with multiple doses of IONIS-FB-L_{Rx} during a six-week period resulted in greater reductions in circulating FB levels. In this study, IONIS-FB-L_{Rx} demonstrated a favorable safety and tolerability profile.

We and Roche are collaborating to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases. In June 2019, we initiated a Phase 2 study evaluating IONIS-FB-L_{Rx} in patients with geographic atrophy secondary to age-related macular degeneration. The study is a randomized, masked, placebo-controlled study designed to assess the safety, tolerability and pharmacokinetics of multiple ascending doses of IONIS-FB-L_{Rx} administered subcutaneously in adults with geographic atrophy.

In September 2019, we initiated a Phase 2 study of IONIS-FB-L_{Rx} in patients with IgA nephropathy. The current study is a single-arm, open-label study designed to assess the safety, tolerability and pharmacokinetics of IONIS-FB-L_{Rx} administered subcutaneously in adults with primary IgA nephropathy.

ION357 – ION357 (IONIS-RHO-2.5_{Rx}), is an investigational antisense medicine we designed to treat patients with a genetic form of autosomal dominant retinitis pigmentosa by inhibiting the production of the rhodopsin P23H mutant protein in the eye while allowing normal protein to be expressed.

Retinitis pigmentosa, or RP, is a group of rare inherited eye disorders causing photoreceptor degeneration that leads to progressive vision loss. Photoreceptors are cells in the eye's retina responsible for converting light into signals that are sent to the brain. Photoreceptors provide us our color and night vision. Affected patients first experience defective dark adaptation during adolescence or young adulthood, followed by loss of peripheral visual field. Patients eventually have limited residual central vision, which ultimately leads to complete blindness around the age of 60.

We and ProQR are collaborating to develop ION357 to treat patients with RP. In November 2019, ProQR initiated a Phase 1/2 clinical study evaluating ION357 in patients with RP. The current study is a randomized, masked, placebo-controlled study designed to assess the safety and tolerability of ION357 in adult patients with RP.

Phase 1 Medicines in Clinical Development

The efficiency and broad applicability of our technology enables us to develop medicines for a broad range of diseases. In 2020, we initiated six Phase 1 or Phase 1/2 studies.

IONIS' Phase 1 and Preclinical Pipeline

IONIS CLINICAL PIPELINE – PHASE 1 AND PRECLINICAL					
	MEDICINES	INDICATION	PARTNER	PRECLINICAL	PHASE 1
NEUROLOGICAL					
	ION363	FUS-ALS	Ionis		
	ION716	Prion disease	Ionis		
	ION582	Angelman syndrome	Biogen		
	ION260	Neurological disease	Biogen		
	ION283	Lafora disease	Ionis		
	ION373	Alexander disease	Ionis		
CARDIOMETABOLIC					
	ION532	Kidney disease	AstraZeneca		
	ION904	TRH	Ionis		
	ION839	NASH	AstraZeneca		
	ION224	NASH	Ionis		
	ION547	Cardiometabolic disease	Ionis		
CANCER					
	ION537	Cancer	MD Anderson		
	ION251	Multiple Myeloma	Ionis		
	ION929	Cancer	Ionis		
	ION674	Lymphomas	Suzhou-Ribo		
PULMONOLOGY AND ALLERGY					
	ION663	Pulmonary	Ionis		
OTHER					
	ION253	GI Autoimmune disease	Janssen		

Antisense Technology

Our antisense technology is an innovative platform for discovering first-in-class and/or best-in-class medicines and represents an important advance in the way we treat disease. Antisense medicines target RNA, the intermediary that conveys genetic information from a gene to the protein synthesis machinery in the cell. By targeting RNA instead of proteins, we can use antisense technology to increase, decrease or alter the production of specific proteins. The unique properties of antisense technology provide several advantages over traditional drug discovery technologies.

These advantages include:

- Direct intervention in the disease process at the genetic level by targeting RNA: antisense technology represents a direct route from gene to drug. The explosion in genomic information and RNA biology has led to the discovery of many new disease-causing proteins and RNAs and has created new opportunities that are uniquely accessible by antisense technology.
- Precise specificity: we design antisense medicines to target a single RNA, which minimizes the possibility of binding to unintended targets, which can cause unwanted side effects.
- Good drug properties: antisense medicines distribute well throughout the body without the need for special formulations or vehicles. They also have a long half-life, in the range of weeks to months, which means patients and/or healthcare providers can dose our medicines weekly, monthly or even less frequently depending on the medicine and target tissue.
- Ability to combine with other medicines: because antisense medicines do not interact with the enzymes that metabolize or break down other medicines, physicians can use our medicines in combination with other medicines.
- Broad applications to multiple disease targets, multiple tissues and multiple mechanisms: there are virtually no “undruggable” targets with antisense technology.
- Efficient discovery and early development: because of the efficiency of our antisense technology, our drug discovery and early development costs and success rates compare favorably to small molecule or antibody drug discovery and development.

We develop antisense medicines we believe will pioneer new markets and change standards of care across a wide range of diseases, including neurological and cardiometabolic diseases.

Technology Overview

We use our core technology platform to discover and develop medicines that affect targets in the body at the genetic level. Genes contain the information necessary to produce proteins. A gene is made up of nucleotides containing the nucleoside bases: adenine, thymine, guanine, and cytosine, commonly known as A, T, G and C, which are linked together to form a two-stranded structure that resembles a twisted ladder, known as DNA. The nucleotides on one side of the ladder bind weakly to complementary nucleotides on the other strand according to specific rules; for example, A pairs with T and G pairs with C, creating the ladder's rungs (Figure 1). Scientists call this highly specific nucleotide pairing hybridization. The sequence or order of these nucleotides establishes the cell's recipes for making proteins. Each protein's instructions reside in a corresponding segment of DNA known as a gene.

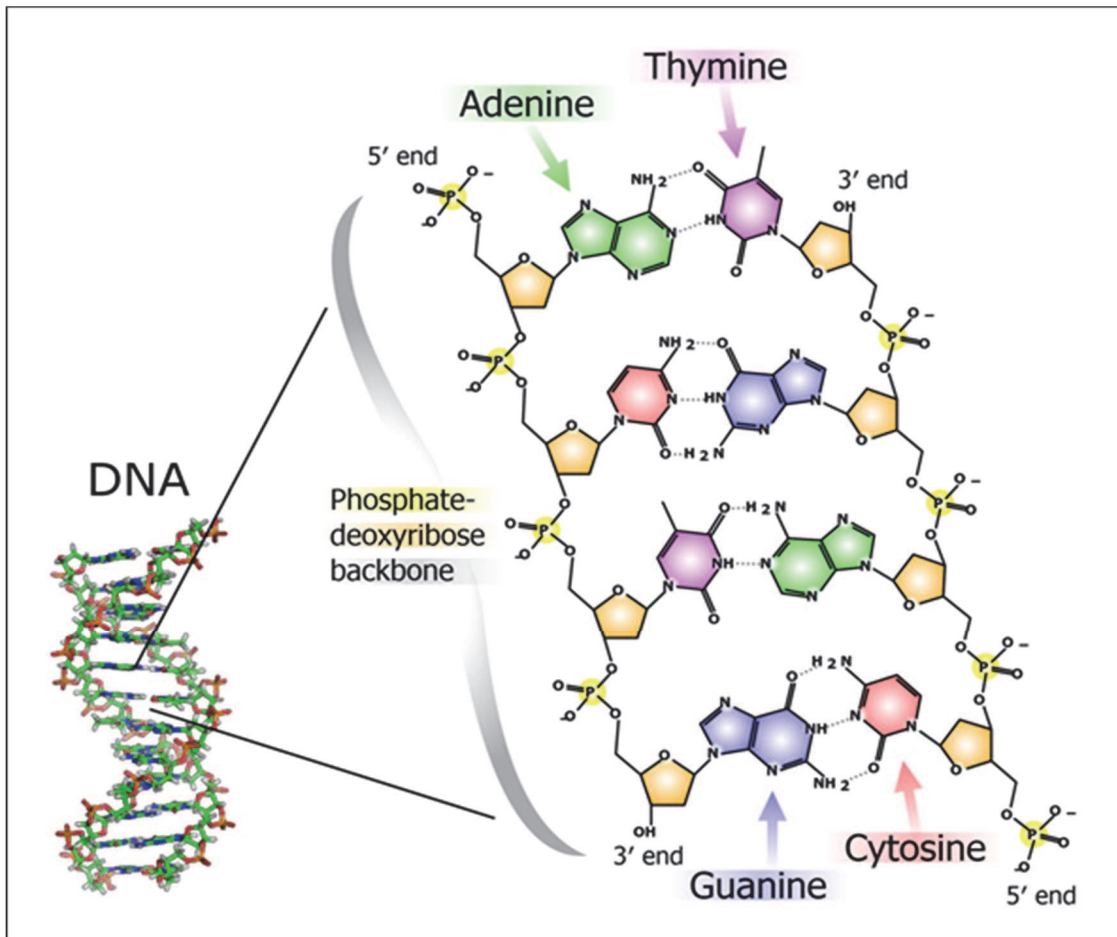


Figure 1: Illustration of DNA.

The instructions for making a protein are transcribed from a gene, or DNA, into a different genetic molecule called messenger RNA. This process starts with the partial uncoiling of the two complementary strands of the DNA. One strand acts as a template and information stored in the DNA template strand is copied into a complementary RNA (Figure 2) by an enzyme called RNA polymerase, or RNAP. Messenger RNA, or mRNA, are mature, fully processed RNA that code for proteins.

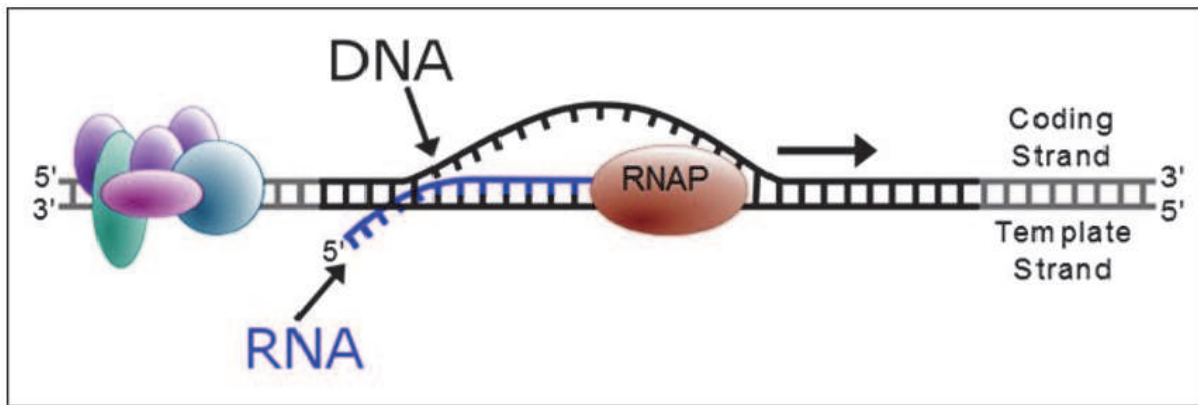


Figure 2: Transcription of information contained in a gene, or DNA, to RNA.

Ribosomes, the cell's factories for manufacturing proteins, translate mRNA into proteins. The ribosome reads the encoded information, the mRNA's nucleotide sequence, and in doing so, strings together amino acids to form a specific protein (Figure 3).

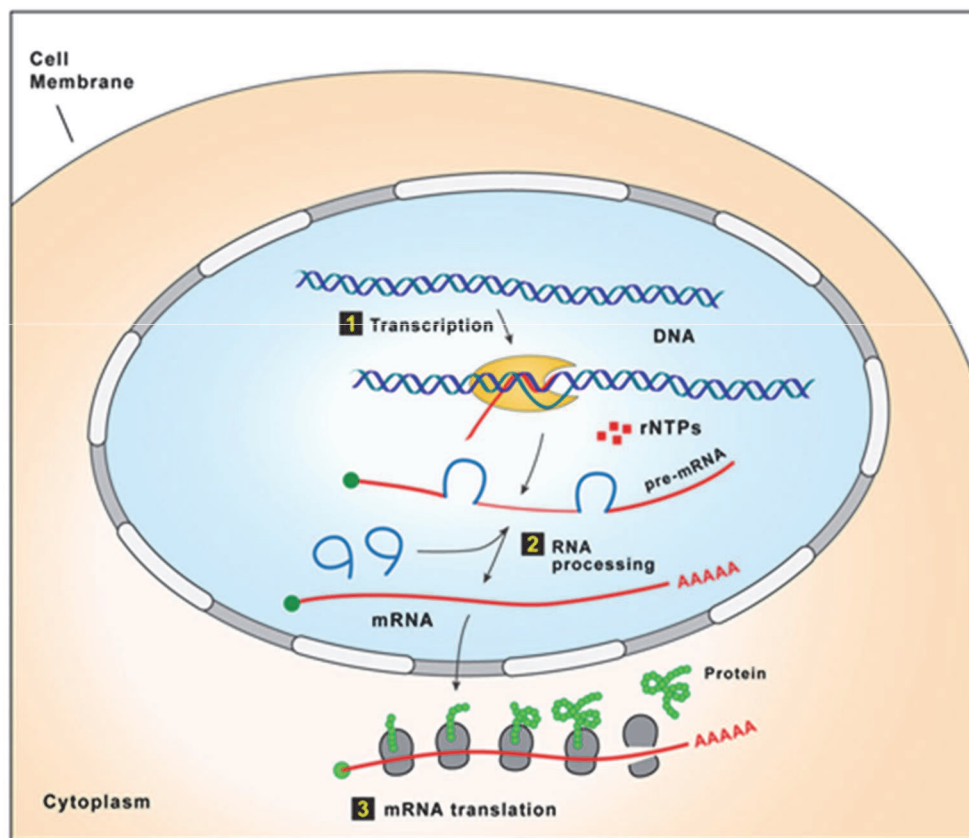


Figure 3: Translation of the protein-coding information contained in mRNA to protein.

We primarily use our antisense technology to interrupt the cell's protein production process by preventing the mRNA instructions from reaching the ribosome, thus inhibiting the production of the protein. We can also design antisense medicines to increase protein production for diseases caused by the lack of a particular protein or modify the processing (or splicing) of the mRNA, which can alter the composition of the protein. The mRNA sequence of nucleotides that carries the information for protein production is called the 'sense' strand. Scientists call the complementary nucleotide chain that binds specifically to the sense strand the "antisense" strand. We use the information contained in mRNA to design chemical structures, that we call antisense oligonucleotides, or ASOs, or antisense medicines, which resemble DNA and RNA and are the complement of RNA. Our antisense medicines bind with high selectivity to the mRNA they were designed to target. Since each mRNA codes for a specific protein, we can design antisense medicines that selectively inhibit the disease-causing member of a protein family without interfering with other members of the protein family that might be necessary for normal cellular or bodily functions. This unique specificity means that antisense medicines may be less toxic than traditional medicines because we can design them to minimize the impact on unintended targets.

We have developed the majority of the medicines in our pipeline using our advanced screens to produce medicines with what we believe have the best possible safety and tolerability profiles. We continue to advance our antisense technology to create even more potent medicines that we can use in more tissues and against more targets. These advances allow us to expand the mechanisms through which we can use our medicines and provide us with greater opportunities to use our antisense medicines to treat a greater number of diseases and reach more patients. Today our medicines and those entering our pipeline utilize our key technology advances, including our next generation chemistry, Generation 2.5, and our LICA technology.

Generation 2.5 chemistry, used in several medicines in our pipeline, enables up to 10-fold greater potency compared to our medicines using our earlier chemistries. This increased potency enables broad distribution throughout the body and target engagement to multiple tissues including liver, kidney, lung, muscle, adipose, adrenal gland, peripheral nerves and tumor tissues. Our Generation 2.5 medicines constitute some of the new medicines we recently added to our pipeline.

LICA is a chemical technology we developed that involves attaching a molecule called a ligand that binds with receptors on the surfaces of cells in a highly specific manner. Because these receptors are often found only on certain cell types, LICA allows us to increase effective delivery of our antisense medicines with higher specificity to certain cell types that express these receptors relative to non-conjugated antisense medicines. As of December 2020, we have an integrated assessment of data from multiple LICA medicines and over 1,200 subjects who have been treated with our LICA medicines, which demonstrates that our LICA technology for liver targets can increase potency by 20-30-fold over our non-LICA antisense medicines.

In addition to the increase in potency, the LICA platform has consistently demonstrated favorable safety and tolerability. Pelacarsen exemplifies these improvements. We designed this medicine to reduce the production of Apo(a) protein in the liver to offer a direct approach for reducing Lp(a). Pelacarsen was the first and only medicine to selectively and robustly reduce Lp(a) levels below threshold levels associated with CVD in nearly all patients and demonstrated a favorable safety and tolerability profile in the Phase 2 study. The study included more than 280 patients, with 98 percent of patients in the high dose group achieving levels below 50 mg/dL, the recognized risk threshold for CVD.

We can also combine our LICA technology with our Generation 2.5 chemistry, further increasing potency. This increase in potency may enable oral delivery of our antisense medicines. In addition to the LICA technology for liver targets, we are also developing LICA conjugation technology that we can use to target other tissues, such as muscle, and initial results are promising.

Antisense Targets and Mechanisms

There are more than a dozen different antisense mechanisms that we can utilize with our antisense technology. The majority of the medicines in our pipeline bind to mRNAs and inhibit the production of disease-causing proteins. However, our antisense technology is broadly applicable to many different antisense mechanisms, including modulation of RNA splicing, RNA interference, or RNAi, and enhancing protein translation to increase protein production.

When using antisense technology to inhibit the production of disease-causing proteins or reduce levels of harmful RNAs, our antisense medicines bind to the target RNA via highly specific nucleotide pairing, or hybridization, and recruit a cellular enzyme called ribonuclease H1, or RNase H1, to degrade the target RNA. The antisense medicine itself remains intact during this process, so it can remain active against additional target RNA molecules and repeatedly trigger their degradation (Figure 4). Examples of our antisense medicines that use the RNase H1 mechanism to reduce disease protein production include, TEGSEDI, WAYLIVRA, tominersen, pelacarsen, and others.

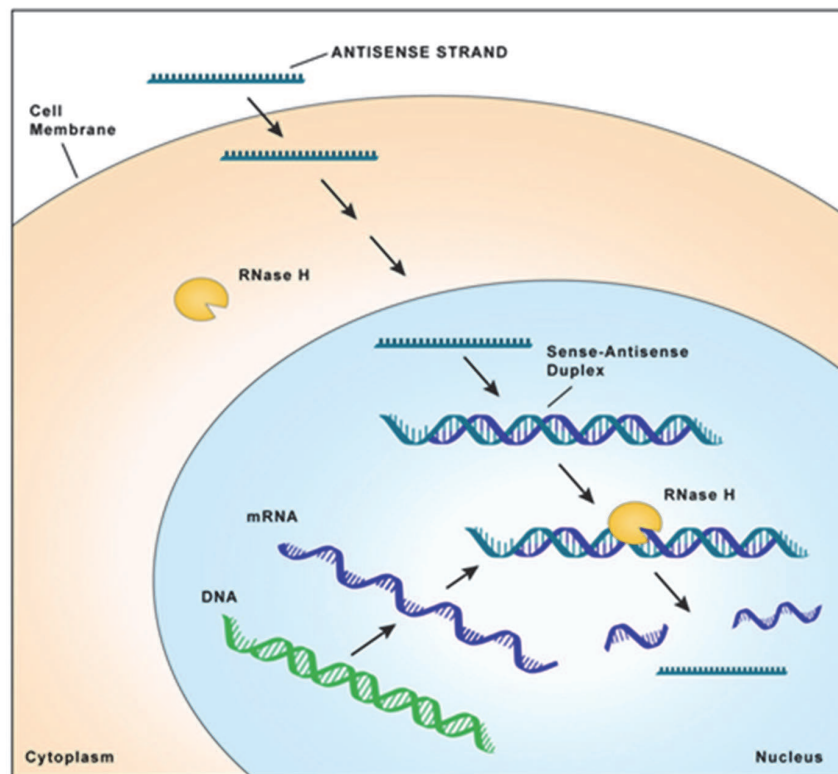


Figure 4: Antisense medicine using the RNase H mechanism of action.

SPINRAZA is an example of an antisense medicine that modulates RNA splicing to increase protein production of the SMN protein (Figure 5), which is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuro-muscular function. The SMN protein is deficient in people with SMA. There are a number of other diseases, including cystic fibrosis and Duchenne muscular dystrophy, which may be treated by modulating splicing using antisense technology.

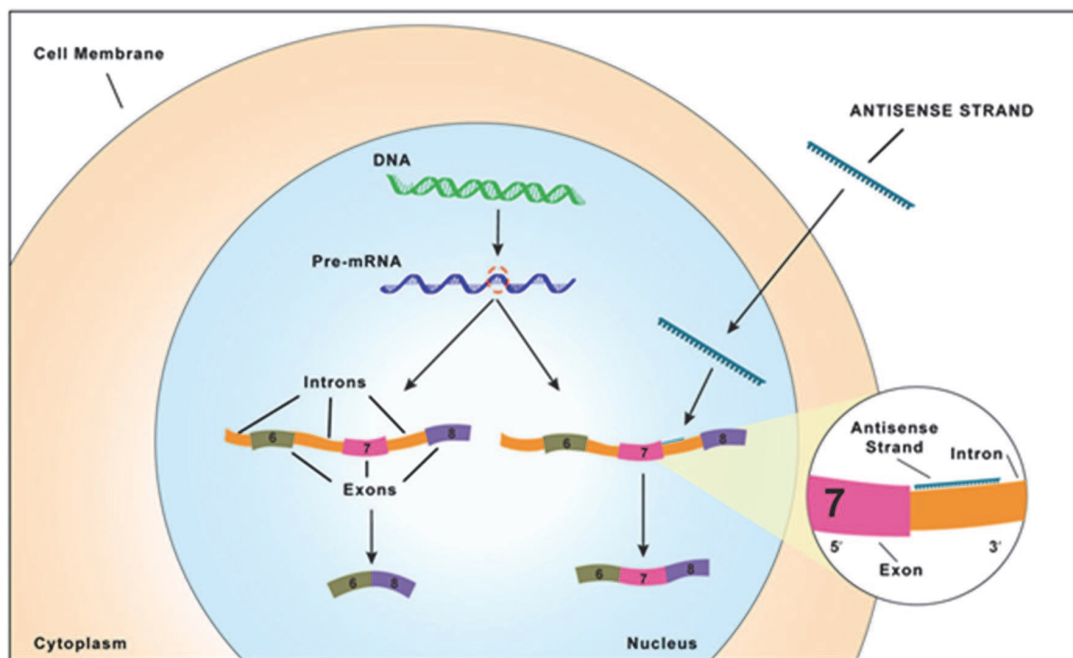


Figure 5: Antisense medicine altering splicing of the SMN2 mRNA.

We are also making progress in designing antisense medicines to target long, non-coding RNAs, or lncRNAs and RNAs that possess a toxic function in human diseases. Many of these RNAs, such as lncRNAs, do not make proteins but often cause disease by regulating the function of other genes or proteins. In 2014, we published a paper in *Nature* in which we were the first to show that targeted reduction of a lncRNA with an antisense compound can ameliorate certain cognitive deficits in a mouse model of Angelman syndrome, or AS. Moreover, these studies demonstrate the potential therapeutic benefits of antisense medicines for the treatment of AS.

Because the efficiency of our core technology platform can support multiple target-based antisense research programs, we can develop antisense medicines to target a broad range of diseases, efficiently producing a large and broad proprietary portfolio of medicines. We are currently pursuing antisense drug discovery programs focused on neurological, cardiometabolic, and other diseases.

Collaborative Arrangements

We have established alliances with a cadre of leading global pharmaceutical companies. Our partners include the following companies, among others: AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis, Pfizer and Roche. Through our partnerships, we have earned both commercial revenue and a broad and sustaining base of R&D revenue in the form of license fees, upfront payments and milestone payments. In 2020, we recognized nearly \$730 million in revenue, the majority of which was from our partnered medicines and programs. We have the potential to earn more than \$20 billion in future milestone payments, licensing fees and other payments from our current partnerships, not including potential royalties. Below, we include the significant terms of our collaboration agreements. For additional details, including other financial information, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with

Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. We and Biogen are currently developing eight investigational medicines to treat neurodegenerative diseases under these collaborations, including medicines in development to treat people with ALS, Alzheimer's disease and Parkinson's disease. In addition to these medicines, our collaborations with Biogen include a substantial research pipeline that addresses a broad range of neurological diseases. From inception through December 2020, we have received \$2.8 billion from our Biogen collaborations.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. SPINRAZA is approved in over 50 countries around the world. From inception through December 2020, we generated more than \$1.3 billion in total revenue under our SPINRAZA collaboration, including more than \$930 million in revenue from SPINRAZA royalties and more than \$435 million in R&D revenue. We are receiving tiered royalties ranging from 11 percent to 15 percent on sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on net sales of SPINRAZA. Biogen is responsible for global development, regulatory and commercialization activities and costs for SPINRAZA.

New antisense medicines for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen has the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for global development, regulatory and commercialization activities and costs for such therapies. Under the collaboration agreement, we received a \$25 million upfront payment in December 2017. We will receive development and regulatory milestone payments from Biogen if new medicines advance towards marketing approval. In total over the term of our collaboration, we are eligible to receive up to \$1.2 billion in license fees, milestone payments and other payments. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales from any product that Biogen successfully commercializes under this collaboration.

Neurology Collaborations

2018 Strategic Neurology

In April 2018, we and Biogen entered into a strategic collaboration to develop novel antisense medicines for a broad range of neurological diseases and entered into a Stock Purchase Agreement, or SPA. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for these diseases for 10 years. We are responsible for the identification of antisense drug candidates based on selected targets. Biogen is responsible for conducting IND-enabling toxicology studies for the selected medicine. Biogen will have the option to license the selected medicine after it completes the IND-enabling toxicology study. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. In the second quarter of 2018, we received \$1 billion from Biogen, comprised of \$625 million to purchase our stock at an approximately 25 percent cash premium and \$375 million in an upfront payment. We are eligible to receive up to \$270 million in milestone payments for each medicine that achieves marketing approval. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales from any product that Biogen successfully commercializes under this collaboration. We are advancing eight programs under this collaboration and through December 2020, we have generated over \$1.05 billion in payments.

2013 Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license medicines resulting from this collaboration. We will usually be responsible for drug discovery and early development of antisense medicines and Biogen will have the option to license antisense medicines after

Phase 2 proof-of-concept. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. We are currently advancing six investigational medicines in development under this collaboration, including a medicine for Parkinson's disease, three medicines for ALS, a medicine for multiple system atrophy and a medicine for an undisclosed target. In December 2018, Biogen exercised its option to license our most advanced ALS medicine, tofersen, and as a result Biogen is now responsible for global development, regulatory and commercialization activities and costs for tofersen.

Under the terms of the agreement, we received an upfront payment of \$100 million and are eligible to receive milestone payments, license fees and royalty payments for all medicines developed under this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately \$260 million in a license fee and milestone payments per program. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that Biogen successfully commercializes under this collaboration. Through December 2020, we have generated over \$270 million under this collaboration, including \$28 million we received from Biogen in 2020 when Biogen initiated Phase 1/2 trials for ION464, our investigational medicine for MSA and Parkinson's disease and ION541, our investigational medicine for ALS.

2012 Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense medicines to treat neurodegenerative diseases. We are responsible for the development of each of the medicines through the completion of the initial Phase 2 clinical study for such medicine. Biogen has the option to license a medicine from each of the programs through the completion of the first Phase 2 study for each program. Under this collaboration, we are currently advancing IONIS-MAPT_{Rx} for Alzheimer's disease and ION582 for Angelman syndrome. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. In December 2019, Biogen exercised its option to license IONIS-MAPT_{Rx} and as a result Biogen is now responsible for global development, regulatory and commercialization activities and costs for IONIS-MAPT_{Rx}.

Under the terms of the agreement, we received an upfront payment of \$30 million. Over the term of the collaboration, we are eligible to receive up to \$210 million in a license fee and milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that Biogen successfully commercializes under this collaboration. Through December 2020, we have generated over \$155 million under our collaboration, including \$19.5 million we received from Biogen for advancing IONIS-MAPT_{Rx} during 2020.

Research, Development and Commercialization Partners

AstraZeneca

We have two collaborations with AstraZeneca, one focused on the treatment of cardiovascular, renal and metabolic diseases and a second focused on the treatment of oncology diseases. We and AstraZeneca are currently developing several medicines under these collaborations, including medicines in development to treat people with cardiovascular disease, a genetically associated form of kidney disease, nonalcoholic steatohepatitis, or NASH, and cancer. From inception through December 2020, we have generated more than \$380 million from our AstraZeneca collaborations.

Cardiovascular, Renal and Metabolic Diseases Collaboration

In July 2015, we and AstraZeneca formed a collaboration to discover and develop antisense therapies for treating cardiovascular, renal and metabolic diseases. Under our collaboration, AstraZeneca has licensed four medicines from us:

- ION449 (formerly IONIS-AZ4-2.5-L_{Rx}), an investigational medicine we designed to reduce the liver production of PCSK9 and lower the plasma level of LDL-C and thus reduce the risk of cardiovascular disease;
- ION532, an investigational medicine we designed to reduce the production of APOL1 for the treatment of APOL1-associated chronic kidney disease;

- ION839, an investigational medicine we designed to inhibit the production of PNPLA3 protein, a major genetic determinant of NASH progression; and
- ION455, an investigational medicine we designed as a potential treatment for NASH.

AstraZeneca is responsible for global development, regulatory and commercialization activities and costs for each of the medicines it has licensed and any medicines AstraZeneca licenses in the future.

Under the terms of the agreement, we received a \$65 million upfront payment. We are eligible to receive license fees and milestone payments of up to more than \$5.5 billion as medicines under this collaboration advance. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. Through December 2020, we have generated over \$235 million in payments, including \$30 million we earned in 2020 when AstraZeneca licensed ION455 and \$30 million in milestone payments we earned in 2020 when AstraZeneca advanced ION532 and ION449 in development.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense medicines to treat cancer. We and AstraZeneca also established an oncology research program. AstraZeneca has the option to license medicines resulting from the program, and if AstraZeneca exercises its option to license a medicine, it will be responsible for global development, regulatory and commercialization activities and costs for such medicine. In 2020, AstraZeneca licensed ION736, an investigational medicine in development targeting FOXP3 for the treatment of cancer.

Under the terms of this agreement, we received \$31 million in upfront payments. We are eligible to receive license fees and milestone payments of up to more than \$265 million as this collaboration advances. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. Through December 2020, we have generated over \$140 million in payments under this collaboration, including \$13 million we earned in 2020 when AstraZeneca licensed ION736.

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI_{Rx} for the prevention of thrombosis and we received a \$100 million upfront payment. In February 2017, we amended our agreement and Bayer licensed IONIS-FXI-L_{Rx}. In conjunction with the amendment, we received a \$75 million payment. In October 2019, Bayer decided it would advance IONIS-FXI-L_{Rx} following positive clinical results. Bayer is now responsible for all global development, regulatory and commercialization activities and costs for the FXI program. We are eligible to receive additional milestone payments as the FXI program advances toward the market. Over the term of the collaboration, we are eligible to receive up to \$385 million in license fees, milestone payments and other payments. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of both medicines combined. Through December 2020, we have generated over \$185 million under this collaboration.

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new medicines against targets for serious and rare diseases, including infectious diseases and some conditions causing blindness. Under the collaboration, we received upfront payments of \$35 million. Our collaboration with GSK covers hepatitis B virus, including IONIS-HBV_{Rx}, which we designed to reduce the production of viral proteins associated with HBV infection. In the third quarter of 2019, following positive Phase 2 results, GSK licensed our HBV program. GSK is responsible for all global development, regulatory and commercialization activities and costs for the HBV program.

Under our agreement, if GSK successfully develops these medicines and achieves pre-agreed sales targets, we could receive license fees and milestone payments of up to \$262 million. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that GSK successfully commercializes under this alliance. Through December 2020, we have generated over \$185 million in payments under our collaboration.

Janssen Biotech, Inc.

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense medicines that can be locally administered, including oral delivery, to treat autoimmune disorders of the GI tract. Under our collaboration, Janssen is currently advancing ION253 for the treatment of immune-mediated GI disease. Janssen licensed ION253 in November 2017. Prior to Janssen's license of ION253, we were responsible for the discovery activities to identify development candidates. Under our agreement, Janssen is responsible for global development, regulatory and commercialization activities and costs for ION253.

Under the terms of the agreement, we received \$35 million in upfront payments. In addition, we are eligible to receive tiered royalties up to the near teens on net sales from any product that Janssen successfully commercializes under this collaboration. We are eligible to receive up to \$285 million in milestone payments and license fees for ION253. Through December 2020, we have generated over \$80 million under our collaboration, including \$5 million we earned in the third quarter of 2020 when Janssen initiated a Phase 1 trial for ION253.

Novartis

In January 2017, we initiated a collaboration with Novartis to develop and commercialize pelacarsen. We received a \$75 million upfront payment in the first quarter of 2017. In February 2019, Novartis licensed pelacarsen and we earned a \$150 million license fee. Novartis is responsible for conducting and funding future development and regulatory activities for pelacarsen, including a global Phase 3 cardiovascular outcomes study, which Novartis initiated in December 2019. In connection with Novartis' license of pelacarsen, we and Novartis established a more definitive framework under which the companies would negotiate the co-commercialization of pelacarsen in selected markets. Included in this framework is an option by which Novartis could solely commercialize pelacarsen in exchange for Novartis paying us increased sales milestone payments based on sales of pelacarsen.

Under the collaboration, we are eligible to receive up to \$675 million in milestone payments related to pelacarsen. We are also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of pelacarsen. Through December 2020, we have generated approximately \$250 million under our collaboration in upfront payments, milestone payments, license fees and other payments from this collaboration.

In conjunction with this collaboration, we entered into a SPA with Novartis. As part of the SPA, Novartis purchased 1.6 million shares of our common stock for \$100 million in the first quarter of 2017 and purchased \$50 million of Akcea's common stock at the IPO price concurrent with Akcea's IPO in July 2017.

Pfizer

In October 2019, we entered into a license agreement with Pfizer for vupanorsen, an investigational medicine in development to treat people with certain cardiovascular diseases. We completed a Phase 2 study of vupanorsen in patients with elevated levels of triglycerides, or hypertriglyceridemia, type 2 diabetes and NAFLD. Pfizer is responsible for the global development, regulatory and commercialization activities for vupanorsen, subject to our right to co-commercialize in the U.S. and certain additional markets.

Under the terms of the agreement, we received a \$250 million upfront license fee. We are also eligible to receive development, regulatory and sales milestone payments of up to \$1.3 billion and tiered royalties in the mid-teens to low 20 percent range on annual worldwide net sales. Prior to regulatory filing for marketing approval, we have the right, at our option to participate in certain commercialization activities with Pfizer in the U.S. and certain additional markets on pre-defined terms and based on meeting pre-defined criteria. Through December 2020, we have generated over \$330 million, including a \$75 million milestone payment we earned in 2020 when Pfizer began the Phase 2b study of vupanorsen.

PTC Therapeutics

In August 2018, we entered into an exclusive license agreement with PTC to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. Under the license agreement, we are eligible to receive up to \$26 million in payments. We are also eligible to receive royalties from PTC in the mid-20 percent range on net sales in Latin America and certain Caribbean countries for each medicine. PTC's obligation to pay us royalties begins on the earlier of 12 months after the first commercial sale of a product in Brazil or the date that PTC recognizes revenue of at least \$10 million in Latin America. Through December 2020, we have generated over \$20 million under this collaboration.

Roche

Huntington's Disease

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for HD based on our antisense technology. Under the agreement, we discovered and developed tominersen, an investigational medicine targeting HTT protein. We developed tominersen through completion of our Phase 1/2 clinical study in people with early stage HD. In December 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen and is now responsible for the global development, regulatory and commercialization activities and costs for tominersen.

Under the terms of the agreement, we received an upfront payment of \$30 million in April 2013. We are eligible to receive up to \$365 million in a license fee and milestone payments as tominersen advances. In addition, we are eligible to receive up to \$136.5 million in milestone payments for each additional medicine successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on net sales from any product resulting from this alliance. Through December 2020, we have generated \$150 million under our collaboration.

IONIS-FB-L_{Rx} for Complement-Mediated Diseases

In October 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases. We are currently conducting Phase 2 studies in two disease indications for IONIS-FB-L_{Rx}, one for the treatment of patients with GA, the advanced stage of dry AMD, and a second for the treatment of patients with IgA nephropathy. Roche has the option to license IONIS-FB-L_{Rx} at the completion of these studies. Upon licensing, Roche will be responsible for global development, regulatory and commercialization activities and costs.

Under the terms of this agreement, we received a \$75 million upfront payment in October 2018. We are eligible to receive up to \$684 million in milestone payments and license fees. In addition, we are also eligible to receive tiered royalties from the high teens to twenty percent on net sales. Through December 2020, we have generated over \$75 million under our collaboration.

Other Agreements

Alnylam Pharmaceuticals, Inc.

Under the terms of our agreement with Alnylam, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a technology access fee, participation in fees from Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics. In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded antisense therapeutics, ssRNAi therapeutics, and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi medicines targeting a limited number of therapeutic targets on a nonexclusive basis. Additionally, in 2015, we and Alnylam entered into an alliance in which we cross-licensed intellectual property. Under this alliance, we and Alnylam each obtained exclusive license rights to four therapeutic programs. Alnylam granted us an exclusive, royalty-bearing license to its chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against four targets, including FXI and Apo(a) and two other targets. In exchange, we granted Alnylam an exclusive, royalty-bearing license to our chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against four other targets. Alnylam also granted us a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for single-stranded antisense therapeutics. In turn, we granted Alnylam a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for double-stranded RNAi therapeutics.

In the fourth quarter of 2020, we completed an arbitration process with Alnylam. The arbitration panel awarded us \$41 million for payments owed to us by Alnylam related to Alnylam's agreement with Sanofi Genzyme. We recognized the \$41 million payment from Alnylam as R&D revenue in the fourth quarter of 2020.

The Ludwig Institute; Center for Neurological Studies

We have a collaboration with the Ludwig Institute, the Center for Neurological Studies and researchers to discover and develop antisense medicines for ALS and other neurodegenerative diseases. Under this agreement, we

agreed to pay the Ludwig Institute and the Center for Neurological Studies modest milestone payments and royalties on any antisense medicines resulting from the collaboration.

Manufacturing

We manufacture most of the drug product we use for our research and development activities ourselves. We have also manufactured commercial supply for our approved medicines. We have dedicated significant resources to develop ways to improve manufacturing efficiency and capacity. Since we can use variants of the same nucleotide building blocks and the same type of equipment to produce our oligonucleotide medicines, we found that the same techniques we used to efficiently manufacture one oligonucleotide medicine could help improve the manufacturing processes for our antisense medicines. By developing several proprietary chemical processes to scale up our manufacturing capabilities, we have greatly reduced the cost of producing oligonucleotide medicines. For example, we have significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing our capacity to make our medicines. Through both our internal research and development programs and collaborations with outside vendors we may achieve even greater efficiency and further cost reductions.

Our manufacturing facility is located in a 26,800 square foot building in Carlsbad, California. We purchased this building in 2017. In addition, we have a 25,800 square foot building that houses support functions for our manufacturing activities. We lease this facility under a lease that has a term ending in August 2026 with an option to extend the lease for an additional five-year period. Our manufacturing facility is subject to periodic inspections by the FDA and foreign equivalents to ensure that it is operating in compliance with current Good Manufacturing Practices, or cGMP, requirements.

As part of our collaborations we may agree to manufacture clinical trial materials and/or commercial supply for our partners. For example, in the past we have manufactured clinical supply materials for AstraZeneca, Bayer, Biogen, GSK and Novartis and commercial supply materials for Biogen.

We believe we have sufficient manufacturing capacity at our own facility or at contract manufacturing organizations, or CMOs, to meet our current internal research, development and potential commercial needs, as well as our obligations under existing agreements with our partners for research, development and commercial needs. We believe our current network of CMO partners are capable of providing sufficient quantities to meet anticipated commercial demands. Additionally, we continue to evaluate relationships with additional suppliers to increase overall capacity and diversify our supply chain. While we believe that there are alternate sources of supply that can satisfy our commercial requirements, it is possible that identifying and establishing relationships with such sources, if necessary, could result in significant delay or material additional costs. We also could experience a disruption in supply from our current CMO partners.

CMOs are subject to the FDA's cGMP requirements and other rules and regulations prescribed by foreign regulatory authorities. We depend on our CMO partners for continued compliance with cGMP requirements and applicable foreign standards.

Specifically, we have the following in place for our approved medicines, SPINRAZA, TEGSEDI and WAYLIVRA and our medicines in Phase 3 development: tominersen, tofersen, pelacarsen, IONIS-TTR-L_{Rx} and IONIS-APOCIII-L_{Rx}:

SPINRAZA

Since September 2018, Biogen has provided SPINRAZA drug supply. Biogen has an oligonucleotide synthesis manufacturing facility that gives it the capability to manufacture SPINRAZA.

TEGSEDI and WAYLIVRA

For TEGSEDI's commercial drug supply, we are using CMOs to produce custom raw materials, active pharmaceutical ingredient, or API, and finished goods. For WAYLIVRA's commercial drug supply, we have manufactured custom raw materials and API. We are using CMOs to produce the finished goods for WAYLIVRA. Our CMO partners have extensive technical expertise and cGMP experience. We believe our current network of CMO partners are capable of providing sufficient quantities to meet anticipated commercial demands.

Tominersen

Pursuant to our collaboration with Roche, Roche is responsible for tominersen drug supply.

Tofersen

We provided Biogen with the first batch of API for tofersen in 2015 to support the first in human studies under our collaboration agreement with Biogen. Pursuant to our collaboration with Biogen, Biogen is responsible for tofersen drug supply. Biogen has an oligonucleotide synthesis manufacturing facility that gives it the capability to manufacture tofersen for all subsequent clinical studies and potential commercialization, including providing the API for the current Phase 3 study.

Pelacarsen

We supplied the API and the finished drug product for pelacarsen’s Phase 3 study. Pursuant to our collaboration with Novartis, Novartis is responsible for any further pelacarsen drug supply.

Wholly Owned Phase 3 Medicines: IONIS-TTR-L_{Rx}, IONIS-APOCIII-L_{Rx}

We have supplied the API and the finished drug product for IONIS-TTR-L_{Rx} and IONIS-APOCIII-L_{Rx} that we believe will be sufficient through the completion of the Phase 3 programs for each medicine. We plan to leverage our relationships with CMOs to procure long-term raw material and drug supplies at competitive prices in the future.

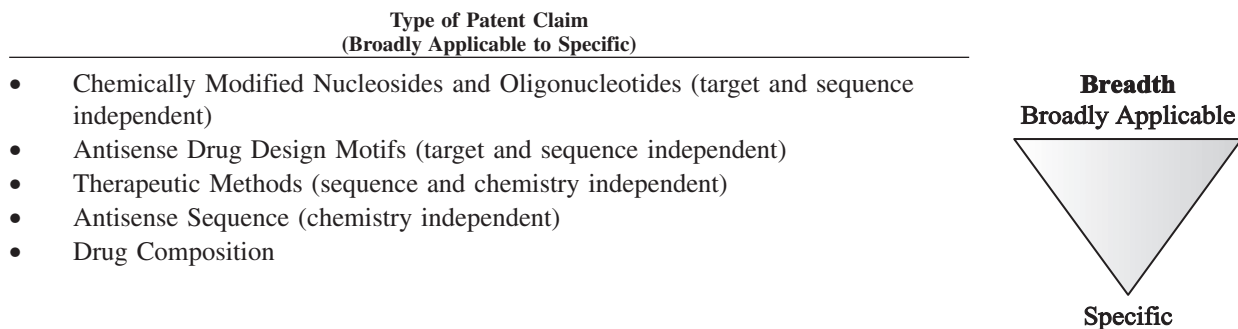
LICA Medicines

We have manufactured and used CMOs to manufacture our LICA medicines for our preclinical and clinical studies. LICA enables lower doses than unconjugated oligonucleotides. With our expertise in optimizing manufacturing of oligonucleotides, we believe we can scale up manufacturing of our LICA medicines at commercially competitive prices or use CMO’s.

Patents and Proprietary Rights

Our success depends, in part, on our ability to obtain patent protection for our products in the U.S. and other countries. We own or have exclusively licensed a substantial patent estate with numerous issued patents worldwide protecting our products and, more generally, our platform for development and commercialization of oligonucleotide therapeutics. We focus our resources on patents and new patent applications that drive value for our company.

We own or control patents that provide exclusivity for products in our pipeline and patents that provide exclusivity for our core technology in the field of antisense more generally. Our core technology patents include claims to chemically modified nucleosides and oligonucleotides as well as antisense medicine designs utilizing these chemically modified nucleosides. These core claims are independent of specific therapeutic target, nucleic acid sequence, or clinical indication. We also own a large number of patents claiming antisense compounds having nucleic acid sequences complementary to therapeutic target nucleic acids, independent of the particular chemical modifications incorporated into the antisense compound. Most importantly, we seek and obtain issued patent claims to specifically protect each of our medicines. For example, we file and seek to obtain claims covering each drug’s nucleic acid sequence and precise drug design. In sum, we maintain our competitive advantage in the field of antisense technology by protecting our core platform technology and by creating multiple layers of patent protection for each of our specific medicines in development.



Chemically Modified Nucleosides and Oligonucleotides

The most broadly applicable of our patents are those that claim modified nucleosides and oligonucleotides comprising the modified nucleosides that we incorporate into our antisense medicines to increase their therapeutic efficacy. Nucleosides and chemically modified nucleosides are the basic building blocks of our antisense medicines. Therefore claims that cover any oligonucleotide incorporating one of our proprietary modified nucleosides can apply to a wide array of antisense mechanisms of action as well as several therapeutic targets. Of particular note are our patents covering our proprietary 2'-O-(2-methoxy) ethyl, or "MOE," modified nucleosides, incorporated into many of our second-generation development compounds, as well as our constrained-ethyl nucleosides, or "cEt" nucleosides incorporated into our Generation 2.5 compounds. The following are some of our patents in this category in key jurisdictions (U.S., Europe and Japan):

<u>Jurisdiction</u>	<u>Patent No.</u>	<u>Title</u>	<u>Expiration</u>	<u>Description of Claims</u>
United States	7,101,993	OLIGONUCLEOTIDES CONTAINING 2'-O-MODIFIED PURINES	2023	Certain MOE nucleosides and oligonucleotides containing these nucleotides
United States	7,399,845	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
United States	7,741,457	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
United States	8,022,193	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Oligonucleotides containing cEt nucleoside analogs
Europe	1984381	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
Europe	2314594	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Oligonucleotides containing cEt nucleoside analogs and methods of use
Japan	5342881	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
United States	7,569,686	COMPOUNDS AND METHODS FOR SYNTHESIS OF BICYCLIC NUCLEIC ACID ANALOGS	2027	Methods of synthesizing cEt nucleosides

Antisense Drug Design Motifs

We also have patents that claim oligonucleotides comprising antisense drug design motifs, or patterns of nucleoside modifications at specified positions in the oligonucleotide. Patent claims covering our antisense drug design motifs are independent of nucleic acid sequence, so they cover oligonucleotides having the recited motif, regardless of cellular target or clinical indication. The claimed motifs generally confer properties that optimize oligonucleotides for a particular antisense mechanism of action, such as ribonuclease H (RNase H), RNAi, or splicing. We have designed oligonucleotides incorporating motifs, which we refer to as chimeric compounds or gapmers, to exploit the RNase H mechanism to achieve target RNA reduction. Almost all of our medicines in clinical development, including TEGSEDI and WAYLIVRA, but excluding SPINRAZA, contain this gapmer antisense drug design motif. We own a U.S. patent that covers all of our second-generation MOE gapmer antisense medicines until March of 2023.

In addition, we have patent claims to antisense drug design motifs incorporating bicyclic nucleosides, which include both locked nucleic acids, or “LNA” and cEt. In Europe, we have been granted claims drawn to certain gapmer oligonucleotides with bicyclic nucleosides, which include locked nucleic acids in the wings. We have also successfully obtained issued patent claims covering our Generation 2.5 gapmer antisense drug design motifs that incorporate our cEt modified nucleosides. The following patents are some examples of our issued patents in this category in key jurisdictions (U.S., Europe and Japan):

<u>Jurisdiction</u>	<u>Patent No.</u>	<u>Title</u>	<u>Expiration</u>	<u>Description of Claims</u>
United States	7,015,315	GAPPED OLIGONUCLEOTIDES	2023	Gapmer oligonucleotides having 2'-O-alkyl-O-alkyl nucleosides
United States	7,750,131	5'-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Oligonucleotides having 5'-methyl BNA nucleosides
Europe	2092065	ANTISENSE COMPOUNDS	2027	Gapmer oligonucleotides having 2'-modified and LNA nucleosides
Europe	2410053	ANTISENSE COMPOUNDS	2027	Gapmer oligonucleotides having wings comprised of 2'-MOE and bicyclic nucleosides
Europe	2410054	ANTISENSE COMPOUNDS	2027	Gapmer oligonucleotides having a 2'-modified nucleoside in the 5'-wing and a bicyclic nucleoside in the 3'-wing
Japan	5665317	ANTISENSE COMPOUNDS	2027	Gapmer oligonucleotides having wings comprised of 2'-MOE and bicyclic nucleosides
United States	9,550,988	ANTISENSE COMPOUNDS	2028	Gapmer oligonucleotides having BNA nucleosides and 2'-MOE nucleosides
United States	10,493,092	ANTISENSE COMPOUNDS	2028	Gapmer oligonucleotides having BNA nucleosides and 2'-MOE nucleosides and/or 2'-OMe nucleosides
Europe	3067421	OLIGOMERIC COMPOUNDS COMPRISING BICYCLIC NUCLEOTIDES AND USES THEREOF	2032	Gapmer oligonucleotides having at least one bicyclic, one 2'-modified nucleoside and one 2'-deoxynucleoside

Ligand-Conjugated Antisense (LICA) Technology

We also have patent claims to new chemistries created to enhance targeting of antisense medicines to specific tissues and cells to improve a drug's properties. We designed our N-acetyl-galactosamine, or GalNAc, LICA medicines to provide an increase in potency for targets in the liver. We have successfully obtained issued patent claims covering our LICA technology conjugated to any modified oligonucleotide, including gapmers, double-stranded siRNA compounds, and fully modified oligonucleotides. The following patents are some examples of our issued patents in this category:

<u>Jurisdiction</u>	<u>Patent</u>	<u>Title</u>	<u>Expiration</u>	<u>Description of Claims</u>
United States	9,127,276	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE	2034	Preferred THA LICA conjugated to any group of nucleosides, including gapmers, double-stranded siRNA compounds, and fully modified oligonucleotides
United States	9,181,549	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE	2034	Preferred THA conjugate having our preferred linker and cleavable moiety conjugated to any oligomeric compound or any nucleoside having a 2'-MOE modification or a cEt modification
Europe	2991661	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE	2034	Preferred THA LICA conjugated to any group of nucleosides, including gapmers, double-stranded siRNA compounds, and fully modified oligonucleotides

Therapeutic Methods of Treatment and Antisense Drug Sequences

In addition to our broad core patents, we also own hundreds of patents, worldwide, with claims to antisense compounds having particular sequences and compounds directed to particular therapeutically important targets or methods of achieving cellular or clinical endpoints using these antisense compounds. These "Target" patents also include claims reciting the specific nucleic acid sequences utilized by our products, independent of chemical modifications and motifs. In addition, our product-specific patents typically include claims combining specific nucleic acid sequences with nucleoside modifications and motifs. In this way, we seek patent claims narrowly tailored to protect our products specifically, in addition to the broader core antisense patents described above.

SPINRAZA and Survival Motor Neuron

We believe SPINRAZA is protected from generic competition in the U.S. and Europe until at least 2030 by a suite of patents. These issued patents include: (i) patents licensed from the University of Massachusetts drawn to antisense compounds having the sequence of SPINRAZA, independent of chemical modification and uses of such compounds for treating SMA, and (ii) joint patents with Cold Spring Harbor Laboratory claiming fully modified 2'MOE compositions targeting SMN2, including the precise composition of matter of SPINRAZA and methods of using such compositions. We have filed for patent term extension, to potentially extend the term beyond 2030. With Biogen's license of SPINRAZA, we assigned our interest in these patents to Biogen. The table below lists some key issued patents protecting SPINRAZA in the U.S. and Europe:

<u>Jurisdiction</u>	<u>Patent No.</u>	<u>Title</u>	<u>Expiration</u>	<u>Description of Claims</u>
United States	10,266,822	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2025	Methods of increasing exon-7 containing SMN2 mRNA in a cell using an oligonucleotide having the sequence of SPINRAZA
United States	8,110,560	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2025	Methods of using antisense oligonucleotides having sequence of SPINRAZA to alter splicing of SMN2 and/or to treat SMA

<u>Jurisdiction</u>	<u>Patent No.</u>	<u>Title</u>	<u>Expiration</u>	<u>Description of Claims</u>
Europe	1910395	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2026	Sequence and chemistry (full 2'-MOE) of SPINRAZA
Europe	3308788	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2026	Pharmaceutical compositions that include SPINRAZA
United States	7,838,657	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2027	Oligonucleotides having sequence of SPINRAZA
United States	8,361,977	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2030	Sequence and chemistry (full 2'-MOE) of SPINRAZA
United States	8,980,853	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2030	Methods of administering SPINRAZA
United States	9,717,750	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2030	Methods of administering SPINRAZA to a patient
Europe	3449926	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2030	Pharmaceutical compositions that include SPINRAZA for treating SMA
Europe	3305302	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2030	Antisense compounds including SPINRAZA for treating SMA

TEGSEDI and Transthyretin

We believe TEGSEDI is protected from generic competition in the U.S. and Europe until at least 2031. Additional patent applications designed to protect TEGSEDI in other foreign jurisdictions are being pursued. The table below lists some key issued patents protecting TEGSEDI in the U.S. and Europe:

<u>Jurisdiction</u>	<u>Patent No.</u>	<u>Title</u>	<u>Expiration</u>	<u>Description of Claims</u>
United States	8,101,743	MODULATION OF TRANSTHYRETIN EXPRESSION	2025	Antisense sequence and chemistry of TEGSEDI
United States	8,697,860	DIAGNOSIS AND TREATMENT OF DISEASE	2031	Composition of TEGSEDI
United States	9,061,044	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Sodium salt composition of TEGSEDI
United States	9,399,774	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Methods of treating transthyretin amyloidosis by administering TEGSEDI
Europe	2563920	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Composition of TEGSEDI

WAYLIVRA and Apolipoprotein C-III

We have obtained patent claims in the U.S. and Europe drawn to the use of antisense compounds complementary to a broad active region of human ApoC-III, including the site targeted by WAYLIVRA. We have also obtained issued patents claiming the specific sequence and chemical composition of WAYLIVRA in the U.S. and Europe. We believe the issued claims protect WAYLIVRA from generic competition in the U.S. and Europe until at least 2023 and 2024, respectively. We are pursuing additional patent applications designed to protect WAYLIVRA worldwide. The table below lists some key issued patents protecting WAYLIVRA in the U.S. and Europe:

<u>Jurisdiction</u>	<u>Patent No.</u>	<u>Title</u>	<u>Expiration</u>	<u>Description of Claims</u>
United States	9,624,496	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Antisense compounds specifically hybridizable within the nucleotide region of ApoCIII targeted by WAYLIVRA
United States	7,598,227	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Methods of treating hyperlipidemia, lowering cholesterol levels or lowering triglyceride levels with WAYLIVRA
United States	7,750,141	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Antisense sequence and chemistry of WAYLIVRA
Europe	1622597	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2024	Antisense sequence and chemistry of WAYLIVRA
Europe	2441449	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2024	Antisense compounds specifically hybridizable within the nucleotide region of ApoCIII targeted by WAYLIVRA
Europe	3002007	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2024	Compounds complementary to an ApoCIII nucleic acid for use in therapy
United States	9,157,082	MODULATION OF APOLIPOPROTEIN C-III (APOCIII) EXPRESSION	2032	Methods of using ApoCIII antisense oligonucleotides for reducing pancreatitis and chylomicronemia and increasing HDL
United States	9,593,333	MODULATION OF APOLIPOPROTEIN C-III (APOCIII) EXPRESSION IN LIPOPROTEIN LIPASE DEFICIENT (LPLD) POPULATIONS	2034	Methods of treating lipoprotein lipase deficiency with an ApoCIII specific inhibitor wherein triglyceride levels are reduced
Europe	2956176	MODULATION OF APOLIPOPROTEIN C-III (APOCIII) EXPRESSION IN LIPOPROTEIN LIPASE DEFICIENT (LPLD) POPULATIONS	2034	ApoCIII specific inhibitors including WAYLIVRA for treating lipoprotein lipase deficiency or familial chylomicronemia syndrome

Tominersen and Huntingtin

We believe tominersen is protected from generic competition in the U.S. and Europe until at least 2030. Additional patent applications designed to protect tominersen in other foreign jurisdictions are being pursued. The table below lists some key issued patents protecting tominersen in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	7,951,934	COMPOSITIONS AND THEIR USES DIRECTED TO HUNTINGTIN	2027	Antisense sequence of tominersen
United States	8,952,145	COMPOSITIONS AND THEIR USES DIRECTED TO HUNTINGTIN	2027	Antisense compound specifically hybridizable within the nucleotide region of HTT targeted by tominersen
Europe	2161038	COMPOSITIONS AND THEIR USES DIRECTED TO HUNTINGTIN	2027	Antisense sequence of tominersen
United States	9,273,315	MODULATION OF HUNTINGTIN EXPRESSION	2030	Composition of tominersen
United States	8,906,873	MODULATION OF HUNTINGTIN EXPRESSION	2030	Methods of treating Huntington's disease by administering tominersen
Europe	2475675	MODULATION OF HUNTINGTIN EXPRESSION	2030	Composition of tominersen

Tofersen and SOD-1

We believe tofersen is protected from generic competition in the U.S. and Europe until at least 2035. Additional patent applications designed to protect tofersen in other foreign jurisdictions are being pursued. With Biogen's license of tofersen, we assigned our interest in these patents to Biogen. The table below lists some key issued patents protecting tofersen in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	8,993,529	ANTISENSE MODULATION OF SUPEROXIDE DISMUTASE 1, SOLUBLE EXPRESSION	2021	Pharmaceutical compositions that include antisense compounds specifically hybridizable within nucleotide region of SOD-1 targeted by tofersen
Europe	2270024	ANTISENSE MODULATION OF SUPEROXIDE DISMUTASE 1, SOLUBLE EXPRESSION	2022	Antisense compound specifically hybridizable within nucleotide region of SOD-1 targeted by tofersen
United States	10,385,341	COMPOSITIONS FOR MODULATING SOD-1 EXPRESSION	2035	Composition of tofersen
United States	10,669,546	COMPOSITIONS FOR MODULATING SOD-1 EXPRESSION	2035	Methods of treating a SOD-1 associated neurodegenerative disorder by administering tofersen
Europe	3126499	COMPOSITIONS FOR MODULATING SOD-1 EXPRESSION	2035	Composition of tofersen

Pelacarsen and Apo(a)

We believe pelacarsen is protected from generic competition in the U.S. and Europe until at least 2034. Additional patent protection designed to protect pelacarsen in other foreign jurisdictions is being pursued. The table below lists some key issued patents protecting pelacarsen in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	9,574,193	METHODS AND COMPOSITIONS FOR MODULATING APOLIPOPROTEIN (A) EXPRESSION	2033	Methods of lowering Apo(a) and/or Lp(a) levels with an oligonucleotide complementary within the nucleotide region of Apo(a) targeted by pelacarsen
United States	10,478,448	METHODS AND COMPOSITIONS FOR MODULATING APOLIPOPROTEIN (A) EXPRESSION	2033	Methods of treating hyperlipidemia with an oligonucleotide complementary within the nucleotide region of Apo(a) targeted by pelacarsen
United States	9,884,072	METHODS AND COMPOSITIONS FOR MODULATING APOLIPOPROTEIN (A) EXPRESSION	2033	Oligonucleotides complementary within the nucleotide region of Apo(a) targeted by pelacarsen
Europe	2855500	METHODS AND COMPOSITIONS FOR MODULATING APOLIPOPROTEIN (A) EXPRESSION	2033	Oligonucleotides complementary within the nucleotide region of Apo(a) targeted by pelacarsen for decreasing Apo(a) expression
United States	9,181,550	COMPOSITIONS AND METHODS FOR MODULATING APOLIPOPROTEIN (a) EXPRESSION	2034	Composition of pelacarsen
Europe	2992009	COMPOSITIONS AND METHODS FOR MODULATING APOLIPOPROTEIN (a) EXPRESSION	2034	Composition of pelacarsen

IONIS-TTR-L_{Rx} and Transthyretin

We believe IONIS-TTR-L_{Rx} is protected from generic competition in the U.S. and Europe until at least 2034. Additional patent applications to protect IONIS-TTR-L_{Rx} in other foreign jurisdictions are being pursued. The table below lists some key issued patents protecting IONIS-TTR-L_{Rx} in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	10,683,499	COMPOSITIONS AND METHODS FOR MODULATING TTR EXPRESSION	2034	Composition of IONIS-TTR-L _{Rx}
Europe	3524680	COMPOSITIONS AND METHODS FOR MODULATING TTR EXPRESSION	2034	Composition of IONIS-TTR-L _{Rx}

IONIS-APOCIII-L_{Rx}

We believe IONIS-APOCIII-L_{Rx} is protected from generic competition in the U.S. and Europe until at least 2034. Additional patent applications to protect IONIS-APOCIII-L_{Rx} in other foreign jurisdictions are being pursued. The table below lists some key issued patents protecting IONIS-APOCIII-L_{Rx} in the U.S. and Europe.

<u>Jurisdiction</u>	<u>Patent No.</u>	<u>Title</u>	<u>Expiration</u>	<u>Description of Claims</u>
United States	9,163,239	COMPOSITIONS AND METHODS FOR MODULATING APOLIPOPROTEIN C-III EXPRESSION	2034	Composition of IONIS-APOCIII-L _{Rx}
Europe	2991656	COMPOSITIONS AND METHODS FOR MODULATING APOLIPOPROTEIN C-III EXPRESSION	2034	Composition of IONIS-APOCIII-L _{Rx}

We seek patent protection in significant markets and/or countries for each medicine in development. We also seek to maximize patent term. In some cases, the patent term can be extended to recapture a portion of the term lost during FDA regulatory review. The patent exclusivity period for a medicine will prevent generic medicines from entering the market. Patent exclusivity depends on a number of factors including initial patent term and available patent term extensions based upon delays caused by the regulatory approval process.

Manufacturing Patents

We also own patents claiming methods of manufacturing and purifying oligonucleotides. These patents claim methods for improving oligonucleotide drug manufacturing, including processes for large-scale oligonucleotide synthesis and purification. These methods allow us to manufacture oligonucleotides at lower cost by, for example, eliminating expensive manufacturing steps.

We also rely on trade secrets, proprietary know-how and continuing technological innovation to develop and maintain a competitive position in antisense therapeutics.

Government Regulation

Regulation by government authorities in the U.S. and other countries is a significant component in the development, manufacture and commercialization of pharmaceutical products and services. In addition to regulations enforced by the FDA and relevant foreign regulatory authorities, we are also subject to regulation under the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other present and potential future federal, state and local regulations.

Extensive regulation by the U.S. and foreign governmental authorities governs the development, manufacture and sale of our medicines. In particular, our medicines are subject to a number of approval requirements by the FDA in the U.S. under the Federal Food, Drug and Cosmetic Act, or FDCA, and other laws and by comparable agencies in those foreign countries in which we conduct business. The FDCA and other various federal, state and foreign statutes govern or influence the research, testing, manufacture, safety, labeling, storage, recordkeeping, approval, promotion, marketing, distribution, post-approval monitoring and reporting, sampling, quality, and import and export of our medicines. State, local, and other authorities also regulate pharmaceutical manufacturing facilities and procedures.

Our manufacturing facility and our CMOs are subject to periodic inspection by the FDA and other foreign equivalents to ensure that they are operating in compliance with cGMP requirements. In addition, marketing authorization for each new medicine may require a rigorous manufacturing pre-approval inspection by regulatory authorities. Post approval, there are strict regulations regarding changes to the manufacturing process, and, depending on the significance of the change, changes may require prior FDA approval. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use.

The FDA must approve any new medicine before a manufacturer can market it in the U.S. In order to obtain approval, we and our partners must complete clinical studies and prepare and submit an NDA to the FDA. If the FDA approves a medicine, it will issue an approval letter authorizing commercial marketing of the medicine and may

require a risk evaluation and mitigation strategy, or REMS, to help ensure the benefits of the medicine outweigh the potential risks. For example, TEGSEDI has a REMS program. The requirements for REMS can materially affect the potential market and profitability of our medicines. In foreign jurisdictions, the drug approval process is similarly demanding.

For any approved medicine, domestic and foreign sales of the medicine depend, in part, on the availability and amount of coverage and adequate reimbursement by third-party payors, including governments and private health plans. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product, or procedures which utilize such product. Private health plans may seek to manage cost and use of our medicines by implementing coverage and reimbursement limitations. For example, third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of U.S. FDA-approved products for a particular indication. In certain jurisdictions, governments may also regulate or influence coverage, reimbursement and/or pricing of our medicines to control cost or affect use. Within the EU a variety of payors pay for medicines, with governments being the primary source of payment. Negotiating pricing with governmental authorities can delay commercialization. Such pricing and reimbursement factors could impact our ability and that of our commercial partners to successfully commercialize approved medicines. Further, it is possible that additional governmental action is taken in response to the COVID-19 pandemic.

In the U.S. and foreign jurisdictions, the legislative landscape continues to evolve. There have been a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the U.S. federal and state levels and by foreign governments that seek to reduce healthcare costs. There has also been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in efforts to bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for medicines. Further, it is possible that additional governmental action is taken in response to the COVID-19 pandemic.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCA, which regulate the distribution and tracing of prescription drugs and prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Other healthcare laws that may affect our ability to operate include, for example, the following:

- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information;
- Foreign and state laws governing the privacy and security of health information, such as the General Data Protection Regulation, or GDPR, in the EU; and the California Consumer Privacy Act, or CCPA, in California, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect; and
- The Physician Payments Sunshine Act, which requires manufacturers of medicines, devices, biologics, and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians, other healthcare providers and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members.

Sales and Marketing

Numerous regulatory authorities in addition to the FDA, including, in the U.S., the Centers for Medicare and Medicaid Services, other divisions of the U.S. Department of Health and Human Services, the U.S. Department of Justice, and similar foreign, state and local government authorities, regulate sales, promotion and other activities following drug approval. As described above, the FDA regulates all advertising and promotion activities for drugs under its jurisdiction both prior to and after approval. Only those claims relating to safety and efficacy that the FDA

has approved may be used in labeling. Physicians may prescribe legally available drugs for uses that are not described in the drug's labeling and that differ from those we tested and the FDA approved. Such off-label uses are common across medical specialties and often reflect a physician's belief that the off-label use is the best treatment for the patients. The FDA does not regulate the behavior of physicians in their choice of treatments, but FDA regulations do impose stringent restrictions on manufacturers' communications regarding off-label uses. If we do not comply with applicable FDA requirements, we may face adverse publicity, enforcement action by the FDA, corrective advertising, consent decrees and the full range of civil and criminal penalties available to the FDA. Promotion of off-label uses of drugs can also implicate the false claims laws described below.

In the U.S. sales, marketing and scientific/educational programs must also comply with various federal and state laws pertaining to healthcare "fraud and abuse," including anti-kickback laws and false claims laws. Anti-kickback laws make it illegal for a prescription drug manufacturer to solicit, offer, receive, or pay any remuneration in exchange for, or to induce, the referral of business, including the purchase or prescription of a particular drug. Due to the breadth of the statutory provisions, limited statutory exceptions and regulatory safe harbors, and the absence of guidance in the form of regulations and very few court decisions addressing industry practices, it is possible that our practices might be challenged under anti-kickback or similar laws. Moreover, recent healthcare reform legislation has strengthened these laws. For example, the PPACA among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes to clarify that a person or entity does not need to have actual knowledge of this statute or specific intent to violate it. In addition, PPACA clarifies that the government may assert that a claim that includes items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the false claims statutes. False claims laws prohibit anyone from knowingly and willingly presenting, or causing to be presented for payment, to third-party payers (including Medicare and Medicaid) claims for reimbursed drugs or services that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Our activities relating to the sale and marketing of our drugs may be subject to scrutiny under these laws. Violations of fraud and abuse laws may be punishable by criminal and civil sanctions, including fines and civil monetary penalties, the possibility of exclusion from federal healthcare programs (including Medicare and Medicaid) and corporate integrity agreements, which impose, among other things, rigorous operational and monitoring requirements on companies. Similar sanctions and penalties also can be imposed upon executive officers and employees, including criminal sanctions against executive officers under the so-called "responsible corporate officer" doctrine, even in situations where the executive officer did not intend to violate the law and was unaware of any wrongdoing.

Given the significant penalties and fines that can be imposed on companies and individuals if convicted, allegations of such violations often result in settlements even if the company or individual being investigated admits no wrongdoing. Settlements often include significant civil sanctions, including fines and civil monetary penalties, and corporate integrity agreements. If the government were to allege or convict us or our executive officers of violating these laws, our business could be harmed. In addition, private individuals can bring similar actions. Our activities could be subject to challenge for the reasons discussed above and due to the broad scope of these laws and the increasing attention being given to them by law enforcement authorities. Other healthcare laws that may affect our ability to operate include the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information; analogous state laws governing the privacy and security of health information, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, and the Physician Payments Sunshine Act, which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members. Further, there are an increasing number of state laws that require manufacturers to make reports to states on pricing and marketing information. Many of these laws contain ambiguities as to what is required to comply with the laws. Given the lack of clarity in laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state authorities.

Similar rigid restrictions are imposed on the promotion and marketing of drugs in the E.U. and other countries. Even in those countries where we may not be directly responsible for the promotion and marketing of our medicines, if our potential international distribution partners engage in inappropriate activity, it can have adverse implications for us.

The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits certain individuals and entities, including us, from promising, paying, offering to pay, or authorizing the payment of anything of value to any foreign government official, directly or indirectly, to obtain or retain business or an improper advantage. If we violate the FCPA, it could result in large civil and criminal penalties as well as an adverse effect on our reputation, operations, and financial condition. We could also face collateral consequences such as debarment and the loss of export privileges.

Competition

Our Business in General

Some of our medicines may compete with existing therapies for market share and some of our medicines in development may compete for patients in study trials. In addition, there are a number of companies pursuing the development of oligonucleotide-based technologies and the development of pharmaceuticals utilizing these technologies. These companies include biopharmaceutical companies and large pharmaceutical companies acting either independently or together. Our medicines are differentiated from traditional small molecule medicines by their chemistry, how they move in the body, how they act in the body, delivery technology, and formulations.

Our approved products and our products under development address numerous markets. The diseases our medicines target for which we have or may receive marketing authorization will determine our competition. For some of our products, an important factor may be the timing of market introduction of competitive products. Accordingly, the relative speed with which we can develop products, complete the clinical trials and marketing authorization processes and supply commercial quantities of the products to the market are important competitive factors. We expect to compete with products approved for sale based on a variety of factors, including, among other things, product efficacy, safety, mechanism of action, dosing convenience, marketing and sales strategy and tactics, availability, price, and reimbursement.

Below we have included what we believe to be the competitive landscape for our marketed medicines and for the medicines we currently have in Phase 3 trials. We have included medicines that we believe compete or may compete directly with our medicines. We included competitors, potential competitors that are past Phase 1 development or potential competitors that plan to start a pivotal study this year. We do not believe that any medicines meet these criteria to compete with pelacarsen.

SPINRAZA

We consider the following medicines as competitors and potential future competitors to SPINRAZA for the indication of SMA:

<u>Medicine</u>	<u>Company</u>	<u>Medicine Description⁽¹⁾</u>	<u>Phase⁽¹⁾</u>	<u>Route of Administration⁽¹⁾</u>
Onasemnogene abeparvec	Novartis	Gene therapy targeting the genetic root cause of SMA by replacing the missing or nonworking SMN1 gene	Approved for Type 1 infants younger than two years old	Intravenous infusion
Risdiplam	PTC/ Roche/ SMA Foundation	A small molecule medicine that modulates splicing of the SMN2 gene	Approved in the U.S.	Oral

(1) Taken from public documents including respective company press releases, company presentations, and scientific presentations.

In May 2019, onasemnogene abeparvec was approved for the treatment of pediatric patients less than two years of age with SMA including those who are presymptomatic at diagnosis.

In August 2020, the FDA approved risdiplam for the treatment of SMA in adults and children two months of age and older.

TEGSEDI and IONIS-TTR-L_{Rx}

We consider the following medicines as competitors and potential future competitors to TEGSEDI and IONIS-TTR-L_{Rx} for the indication of hATTR amyloidosis and/or ATTR cardiomyopathy:

<u>Medicine</u>	<u>Company</u>	<u>Medicine Description⁽¹⁾</u>	<u>Phase⁽¹⁾</u>	<u>Route of Administration⁽¹⁾</u>
Patisiran	Alnylam	An RNAi medicine formulated with lipid nanoparticles to inhibit TTR mRNA	Approved hATTR/ Phase 3 ATTR-CM	Intravenous infusion
Tafamidis and tafamidis meglumine	Pfizer	A small molecule medicine to stabilize TTR protein	Approved in U.S., EU, Japan and select other markets for hATTR-PN and/or ATTR-CM; indications vary by region	Oral
Vutrisiran	Alnylam	An RNAi medicine conjugated with GalNAC to inhibit TTR mRNA	3	Subcutaneous Injection
Acoramidis	Bridgebio	Small molecule that binds and stabilizes TTR in the blood	3	Oral

(1) Taken from public documents including respective company press releases, company presentations, and scientific presentations.

Our main competition for TEGSEDI is patisiran, marketed by Alnylam Pharmaceuticals. Although patisiran requires intravenous administration by a healthcare provider every three weeks and pre-treatment with steroids, it does not have a boxed warning or REMS as TEGSEDI does.

We believe that Alnylam's patisiran and vutrisiran could compete directly against IONIS-TTR-L_{Rx}, given their transthyretin-silencing profile. While their approved indications vary by market, the transthyretin stabilizers, tafamidis/ tafamidis meglumine, marketed by Pfizer, are currently the only approved products for the treatment of ATTR-CM.

WAYLIVRA and IONIS-APOCIII-L_{Rx}

We believe that the following medicines could compete with WAYLIVRA and IONIS-APOCIII-L_{Rx} in FCS:

<u>Medicine</u>	<u>Company</u>	<u>Medicine Description⁽¹⁾</u>	<u>Phase⁽¹⁾</u>	<u>Route of Administration⁽¹⁾</u>
Lomitapide	Amryt Pharma	Microsomal triglyceride transfer protein (MTP) inhibitor	2	Oral
ARO-APOC3	Arrowhead Pharmaceuticals	Targets APOCIII by utilizing Targeted RNAi Molecule Platform	1/2	Subcutaneous Injections
Gemcabene	NeuroBo Pharmaceuticals	Dicarboxylic acid with antihyperlipidemic activity	2	Oral

(1) Taken from public documents including respective company press releases, company presentations, and scientific presentations.

Tominersen

We believe that the following medicines could compete with tominersen in Huntington's Disease:

<u>Medicine</u>	<u>Company</u>	<u>Medicine Description⁽¹⁾</u>	<u>Phase⁽¹⁾</u>	<u>Route of Administration⁽¹⁾</u>
WVE-120101/ WVE-120102	Wave Life Sciences	Antisense medicines targeting mHTT SNP-1 and SNP-2	1b/2a	Intrathecal Infusion
Selisistat	AOP Orphan	An orally active, selective SIRT1 inhibitor	2	Oral
VX15	Vaccinex	A monoclonal antibody that blocks the activity of SEMA4D	2	Intravenous Infusion
AMT-130	UniQure	HTT-silencing micro- RNA gene therapy	1/2	MRI-guided stereotaxic infusion

(1) Taken from public documents including respective company press releases, company presentations, and scientific presentations.

We believe that Wave Life Sciences' WVE-120101 and WVE-120102, being developed for Huntington's Disease, could compete directly against tominersen. These medicines are antisense medicines administered intrathecally, targeting mHTT SNP-1 and SNP-2, respectively. Wave Life Sciences is currently conducting two simultaneous Phase 1b/2a clinical trials, enrolling adults with early manifest Huntington's disease who carry a single nucleotide polymorphism, or SNP, at the SNP1 and SNP2 location.

UniQure has been developing AMT-130, a gene therapy for Huntington's Disease that consists of an AA5 vector carrying an artificial micro-RNA to target mHTT gene.

Tofersen

We believe that the following medicines could potentially compete with tofersen:

<u>Medicine</u>	<u>Company</u>	<u>Medicine Description⁽¹⁾</u>	<u>Phase⁽¹⁾</u>	<u>Route of Administration⁽¹⁾</u>
Arimoclomol	Orphazyme	Provides cellular protection from abnormal proteins by activating molecular "chaperone" proteins that can repair or degrade the damaged proteins	3	Oral
Ultomiris	Alexion	Anti-C5 monoclonal antibody	3	Intravenous Infusion
Masitinib	AB Science	Selective tyrosine kinase inhibitor	3	Oral
Trehalose	Seelos	A disaccharide that stabilizes proteins and activates autophagy to clear materials from damaged cells	2/3	Intravenous Infusion

(1) Taken from public documents including respective company press releases, company presentations, and scientific presentations.

Employees & Human Capital

As of February 18, 2021, we employed 757 people, the vast majority of whom reside in the United States. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Our average employee turnover rate in 2020 was 11.5 percent, excluding reductions related to the Akcea Acquisition, while the turnover for life sciences/ medical device companies over this period was 21 percent according to a survey published by Radford – an Aon Hewitt Company. Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees. The experience and seniority of our employees is as critical to our future success as it has been to the success we have enjoyed to date.

Collective bargaining agreements do not cover any of our employees, and management considers relations with our employees to be good. We believe that the future will be defined by outstanding people and we are committed to recruiting, developing, motivating, and rewarding them.

We encourage you to visit our website for more detailed information regarding our Human Capital programs and initiatives. Nothing on our website shall be deemed incorporated by reference into this Annual Report on Form 10-K.

Benefits

Employees are rewarded individually on the basis of their responsibilities and accomplishments. We offer fair, competitive compensation and benefits to our employees. In addition to salary and bonus programs, we also offer:

- Comprehensive medical, dental and vision insurance;
- 401(k) matching;
- Stock options, RSUs and Employee Stock Purchase Plan, or ESPP
- Vacation, holiday, sick time and paid time off for volunteering;
- Wellness programs
- Flexible spending accounts for health and dependent day care needs;
- Life, AD&D insurance and long-term disability insurance coverage options; and
- Employee Assistance Program, or EAP

We recognize achievements with salary increases, stock awards, promotions, and bonus opportunities.

Pay Equity

We are committed to paying our employees fairly, regardless of their gender, race, or other personal characteristics. To ensure we are achieving our commitment, we benchmark and evaluate pay based on market data and consider factors such as an employee's role and experience, an employee's performance and internal equity. We also regularly review our compensation practices, both in terms of our overall workforce and individual employees, to ensure our pay is fair and equitable.

In 2018, we engaged an independent third-party expert to perform a pay equity analysis which reviewed pay equity by gender and race. We plan to continue to engage a third-party expert to review pay equity every two to three years, as we determine necessary.

Diversity, Equity and Inclusion

At Ionis, we encourage diversity in our workforce. Prejudicial barriers to human potential and productivity are foreign to our values. We recognize that in order for the full potential of our workforce to be realized, we must cultivate an inclusive culture where all employees feel empowered to contribute fully in an environment that values different perspectives, leading to better ideas and increased innovation.

Training and Development

We designed our training and development programs to help employees gain important Ionis knowledge and develop the skills to be successful. All of our trainings from new hire through senior leader, are focused on the Ionis culture and core principles and learning what we mean when we say: "Working the Ionis Way."

We empower our employees to build rewarding careers at Ionis, driven by a culture of yes that encourages personal and professional employee growth. Ionis offers robust training opportunities with course offerings and events available to every employee regardless of level or function. In addition, employees also have access to Ionis' learning and development library which houses important information on career growth and planning. By supporting our employees, we know that each professional development milestone enables our continued success.

COVID-19 Response

As a company focused on improving the health of people around the world, our priority during the COVID-19 pandemic is the safety of our employees, their families, the healthcare workers who work with us and the patients who rely on our medicines. In order to keep employees safe, the majority of the Ionis workforce began working remotely in March 2020 and is doing so efficiently. We have also provided flexible work arrangements to employees as necessary.

Information about our Executive Officers

The following sets forth certain information regarding our executive officers as of February 18, 2021:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	75	Executive Chairman of the Board of Directors
Brett P. Monia, Ph.D.	59	Chief Executive Officer
C. Frank Bennett, Ph.D.	64	Executive Vice President, Chief Scientific Officer
Onaiza Cadoret-Manier	56	Executive Vice President, Chief Corporate Development and Commercial Officer
Richard S. Geary, Ph.D.	63	Executive Vice President, Chief Development Officer
Elizabeth L. Hougen	59	Executive Vice President, Finance and Chief Financial Officer
Patrick R. O'Neil, Esq.	47	Executive Vice President, Legal & General Counsel, Chief Compliance Officer and Corporate Secretary
Eugene Schneider, M.D.	48	Executive Vice President, Chief Clinical Development Officer
Eric E. Swayze, Ph.D.	55	Executive Vice President, Research

STANLEY T. CROOKE, M.D., Ph.D.

Executive Chairman of Ionis' Board of Directors

Dr. Crooke is a founder of Ionis and became Executive Chairman of our board of directors in January 2020. Dr. Crooke served as Chief Executive Officer and a Director from January 1989 to January 2020. He was elected Chairman of the Board in February 1991. Prior to founding Ionis, from 1980 until January 1989, Dr. Crooke was employed by SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories.

In June 2021, Dr. Crooke will retire from Ionis and our Board of Directors. After his retirement, Dr. Crooke will continue to serve as a scientific advisor to Ionis.

BRETT P. MONIA, Ph.D.

Chief Executive Officer

Dr. Monia was promoted to Chief Executive Officer in January 2020. From January 2018 to December 2019, Dr. Monia served as Chief Operating Officer. From January 2012 to January 2018, Dr. Monia served as Senior Vice President. From February 2009 to January 2012, Dr. Monia served as our Vice President, Drug Discovery and Corporate Development and from October 2000 to February 2009, he served as our Vice President, Preclinical Drug Discovery. From October 1989 to October 2000 he held various positions within our Molecular Pharmacology department.

C. FRANK BENNETT, Ph.D.

Executive Vice President, Chief Scientific Officer

Dr. Bennett has served as Ionis' Executive Vice President, Chief Scientific Officer since April 2020. In January 2020, Dr. Bennett was promoted to Chief Scientific Officer. From January 2006 to December 2019, Dr. Bennett served as Senior Vice President, Antisense Research. From June 1995 to January 2006, Dr. Bennett served as our Vice President, Research. From March 1993 to June 1995, he was Director, Molecular Pharmacology, and from May 1992 to March 1993, he was an Associate Director in our Molecular and Cellular Biology department. Prior to joining Ionis in 1989, Dr. Bennett was employed by SmithKline and French Laboratories in various research positions. He is an external member of the Scientific Advisory Board of Experimental Therapeutics Center in Singapore and the Hereditary Disease Foundation.

ONAIZA CADORET-MANIER

Executive Vice President, Chief Corporate Development and Commercial Officer

Ms. Cadoret-Manier has served as Ionis' Executive Vice President, Chief Corporate Development and Commercial Officer since April 2020. Ms. Cadoret-Manier joined Ionis as Chief Corporate Development and Commercial Officer in January 2020. Prior to joining Ionis, from 2018 to 2019 Ms. Cadoret-Manier was the chief commercial officer for Grail Biosciences, an early detection genomics company. Prior to Grail, Ms. Cadoret-Manier was vice president of the Respiratory Franchise at Genentech where she worked from 2011 to 2018. Ms. Cadoret-Manier also has held multiple senior management positions overseeing corporate strategy, alliances, and marketing and sales for numerous disease areas for Genentech, Pfizer and Amylin Pharmaceuticals.

RICHARD S. GEARY, Ph.D.

Executive Vice President, Chief Development Officer

Dr. Geary has served as Ionis' Executive Vice President, Chief Development Officer since January 2021. From April 2020 to December 2020, Dr. Geary served as our Executive Vice President, Development and from August 2008 to March 2020, was our Senior Vice President, Development. From August 2003 to August 2008, Dr. Geary served as our Vice President, Preclinical Development. From November 1995 to August 2003, he held various positions within the Preclinical Development department. Prior to joining Ionis in 1995, Dr. Geary was Senior Research Scientist and Group Leader for the bioanalytical and preclinical pharmacokinetics group in the Applied Chemistry Department at Southwest Research Institute.

ELIZABETH L. HOUGEN

Executive Vice President, Finance and Chief Financial Officer

Ms. Hougen has served as Ionis' Executive Vice President and Chief Financial Officer since April 2020. From January 2013 to March 2020, Ms. Hougen served as our Senior Vice President, Finance and Chief Financial Officer. From January 2007 to December 2012, Ms. Hougen served as our Vice President, Finance and Chief Accounting Officer and from May 2000 to January 2007, she served as our Vice President, Finance. Prior to joining Ionis in 2000, Ms. Hougen was Executive Director, Finance and Chief Financial Officer for Molecular Biosystems, Inc., a public biotechnology company.

PATRICK R. O'NEIL, Esq.

Executive Vice President, Legal, General Counsel, Chief Compliance Officer and Corporate Secretary

Mr. O'Neil has served as Ionis' Executive Vice President, Legal and General Counsel. Mr. O'Neil also serves as our Chief Compliance Officer and Corporate Secretary. From January 2013 to March 2020, Mr. O'Neil served as our Senior Vice President, Legal and General Counsel. From September 2010 to January 2013, Mr. O'Neil served as our Vice President, Legal and General Counsel and from January 2009 to September 2010, he served as our Vice President, Legal and Senior Transactions Counsel. From October 2001 to January 2009 he held various positions within our Legal department. Prior to joining Ionis, Mr. O'Neil was an associate at Cooley LLP.

EUGENE SCHNEIDER, M.D.

Executive Vice President, Chief Clinical Development Officer

Dr. Schneider was promoted to Executive Vice President and Chief Clinical Development Officer of Ionis in January 2021. From August 2018 to December 2020, Dr. Schneider served as our Senior Vice President, Head of Clinical Development. From April 2015 to July 2018, Dr. Schneider was our Vice President, Clinical Development, Severe and Rare Diseases. Dr. Schneider joined Ionis in December 2013 as Executive Director, Clinical Development. Dr. Schneider has two decades of experience in clinical development primarily in the rare diseases space. Prior to joining Ionis, Dr. Schneider was senior medical director at both Synageva BioPharma and Biovail Technologies Ltd.

ERIC E. SWAYZE, Ph.D.

Executive Vice President, Research

Dr. Swayze has served as Ionis' Executive Vice President, Research since April 2020 and is responsible for leading preclinical antisense drug discovery and antisense technology research. In January 2020, Dr. Swayze was promoted to Senior Vice President of Research. Previously, Dr. Swayze was Vice President of Chemistry and Neuroscience Drug Discovery at Ionis, overseeing the advancement of multiple programs to clinical development. He joined Ionis in 1994 and has contributed to key technology advancements, including Ionis' Generation 2.5 chemistry and LICA technology.

Item 1A. RISK FACTORS

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

Risks Related to the COVID-19 Pandemic

Our business could be materially adversely affected by the effects of health epidemics. To date, we believe the impacts of the recent COVID-19 pandemic on our business are limited and manageable.

Our business could be materially adversely affected by health epidemics in regions where we or our partners are commercializing our medicines, have concentrations of clinical trial sites or other business operations, and could cause significant disruption in the operations of third-party manufacturers and contract research organizations upon whom we rely. For example, since December 2019, a novel strain of coronavirus, SARS-CoV-2, causing a disease referred to as COVID-19, has spread worldwide. In March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic, or the COVID-19 Pandemic, and the U.S. government-imposed restrictions on travel between the U.S., Europe and certain other countries. In addition, the Governor of the State of California and the Governor of the Commonwealth of Massachusetts, the states in which our and Akcea's offices are located, respectively, each declared a state of emergency related to the spread of COVID-19 and issued executive orders that directed residents to stay at home.

In response to these public health directives and orders, we implemented work-from-home policies for most of our employees globally and generally suspended business-related travel. Out of an abundance of caution and to protect the health and welfare of our employees, we continue to maintain work-from-home policies for most of our employees. We believe the effects of these work-from-home and travel policies have thus far had a limited impact on our business.

These public health directives and orders have also impacted our and our partners' sales efforts. For example, some physician and hospital policies that have been put in place as a result of the COVID-19 Pandemic restrict in-person access by third parties, which has in some cases impacted our commercialization efforts for TEGSEDI and WAYLIVRA. Additionally, Biogen has reported that as a result of the COVID-19 Pandemic, SPINRAZA sales revenues have decreased in part because SPINRAZA doses have been delayed due, directly or indirectly, to the COVID-19 Pandemic, and that future SPINRAZA sales revenues may be adversely affected by continued dosing delays. These and similar, and perhaps more severe, disruptions in our or our partner's commercial operations could materially impact our business, operating results and financial condition in the future.

Quarantines, shelter-in-place, executive and similar government orders, or the perception that such orders, shutdowns or other restrictions on the conduct of business operations could occur, could impact personnel at third-party manufacturing facilities in the U.S. and other countries, or the availability or cost of materials, which would disrupt our supply chain.

We have experienced impacts to our clinical trial operations due to the COVID-19 Pandemic; however, we believe such impacts are limited and manageable. Some examples of these impacts include:

- we have experienced some impact on clinical site initiation and patient enrollment due to restrictions imposed as a result of the COVID-19 Pandemic;
 - For example, in March 2020, we instituted a temporary suspension of enrollment for new subjects in our Phase 3 studies of IONIS-TTR-L_{Rx} based on advice from our trial advisory committee; however, enrollment has resumed.
- some patients have not been able to meet protocol requirements, as quarantines have impeded patient movement and interrupted healthcare services;
- we have experienced some delays in site initiations due to principle investigators and site staff focusing on and prioritizing COVID-19 patient care; and
- we have experienced some delays in necessary interactions with regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government or contractor personnel.

The spread of COVID-19 has caused a broad impact globally. While the potential economic impact brought by, and the duration of, the COVID-19 Pandemic may be difficult to assess or predict, it could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID-19 could materially affect our business and has and could continue to affect the value of our securities.

The global COVID-19 Pandemic continues to rapidly evolve. While we have not yet experienced material adverse effects to our business as a result of the COVID-19 Pandemic, the ultimate impact of the COVID-19 Pandemic or a similar health epidemic is highly uncertain and subject to change. As such, we do not yet know the full extent of delays or impacts on our business, our clinical trials, healthcare systems or the global economy as a whole. However, these effects could have a material impact on our operations, and we will continue to monitor the COVID-19 Pandemic closely.

Risks Related to the Commercialization of our Medicines

We have limited experience as a company in commercializing medicines, and we may have to invest significant resources to develop these capabilities. If we are unable to establish effective marketing, sales and distribution capabilities or enter into agreements with third parties to market, sell and distribute our medicines, we may not be able to generate revenue from our medicines.

We have limited experience as a company in the marketing, sale and distribution of pharmaceutical products and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel and effectively manage a geographically dispersed sales and marketing team. Any failure to effectively manage our internal sales, marketing and distribution capabilities would adversely impact the commercialization of our medicines. We may not be able to enter into collaborations or hire consultants or external service providers to assist us in sales, marketing and distribution functions on acceptable financial terms, or at all. Even if we are able to engage third parties to market, sell and distribute our medicines, our product revenues and profitability may be lower if we rely on such third parties for these functions than if we were to perform them on our own. In addition, we likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to market, sell and distribute our medicines effectively. If we are not successful in commercializing our medicines, either on our own or through arrangements with one or more third parties, we may not be able to generate revenue from our medicines.

If the market does not accept our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, we are not likely to generate substantial revenues or become consistently profitable.

Even if our medicines are authorized for marketing, including SPINRAZA, TEGSEDI and WAYLIVRA, our success will depend upon the medical community, patients and third-party payers accepting our medicines as medically useful, cost-effective, safe and convenient. Even when the FDA or foreign regulatory authorities authorize our or our partners' medicines for commercialization, doctors may not prescribe our medicines to treat patients. We and our partners may not successfully commercialize additional medicines.

Additionally, in many of the markets where we or our partners may sell our medicines in the future, if we or our partners cannot agree with the government or other third-party payers regarding the price we can charge for our medicines, then we may not be able to sell our medicines in that market. Similarly, cost control initiatives by governments or third-party payers could decrease the price received for our medicines or increase patient coinsurance to a level that makes our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, economically unviable.

The degree of market acceptance for our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, depends upon a number of factors, including the:

- receipt and scope of marketing authorizations;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our medicines and their potential advantages over competing products;
- cost and effectiveness of our medicines compared to other available therapies;
- patient convenience of the dosing regimen for our medicines; and
- reimbursement policies of government and third-party payers.

Based on the profile of our medicines, physicians, patients, patient advocates, payers or the medical community in general may not accept or use any medicines that we may develop.

For example, the product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis, requires periodic blood and urine monitoring, and TEGSEDI is only available through a Risk Evaluation and Mitigation Strategy, or REMS, program. Our main competition in the U.S. market for TEGSEDI is patisiran, marketed by Alnylam Pharmaceuticals, Inc. Although patisiran requires intravenous administration and pre-treatment with steroids, it does not have a boxed warning or REMS. Additionally, the product label for WAYLIVRA in the EU requires regular blood monitoring. In each case, these label requirements could negatively affect our ability to attract and retain patients for these medicines. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help manage these safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. While we believe we can better maintain patients on TEGSEDI and WAYLIVRA through our patient-centric commercial approach where we plan to have greater involvement with physicians and patients, if we cannot effectively maintain patients on TEGSEDI or WAYLIVRA, including due to limitations or restrictions on our ability to conduct periodic blood and urine monitoring of our patients as a result of the current COVID-19 Pandemic, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

If we or our partners fail to compete effectively, our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, will not contribute significant revenues.

Our competitors engage in drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged in developing antisense technology. Our competitors may succeed in developing medicines that are:

- priced lower than our medicines;
- reimbursed more favorably by government and other third-party payers than our medicines;
- safer than our medicines;
- more effective than our medicines; or
- more convenient to use than our medicines.

These competitive developments could make our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other medicines either on their own or in collaboration with others, including our competitors, to treat the same diseases our own collaborative programs target. Competition may negatively impact a partner's focus on and commitment to our medicines and, as a result, could delay or otherwise negatively affect the commercialization of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies of new pharmaceutical products, in obtaining FDA and other regulatory authorizations of such products and in commercializing such products. Accordingly, our competitors may succeed in obtaining regulatory authorization for products earlier than we do.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization in certain geographic markets of products against targets that are also targets of products in our development pipeline. For example:

- Onasemnogene abeparvovec and risdiplam compete with SPINRAZA;
- Patisiran, tafamidis and tafamidis meglumine compete with TEGSEDI;
- Vutrisiran and AG10 could compete with TEGSEDI and IONIS-TTR-L_{Rx};
- ARO-APOC3, lomitapide and gemcabene could compete with WAYLIVRA and IONIS-APOCIII-L_{Rx};
- WVE-120101/WVE-120102, selistat, VX15 and AMT-130 could compete with tominersen; and
- Arimoclomol, ultomiris, mastinib and trehalose could compete with tofersen.

Specifically, SPINRAZA faces competition from onasemnogene abeparvovec, a new gene therapy product that was approved in the U.S. in May 2019 and in the EU in May 2020 for the treatment of SMA as well as risdiplam, a new oral product for the treatment of SMA that was approved in the U.S. in August 2020. Biogen has disclosed that SPINRAZA revenue has decreased due in part to lower sales volumes as a result of increased competition and that future sales of SPINRAZA may be adversely affected by the commercialization of competing products. SPINRAZA injection for intrathecal use is an antisense medicine indicated for the treatment of SMA patients of all ages approved in over 50 countries.

Additionally, companies that are developing medicines that target the same patient populations as our medicines in development may compete with us to enroll participants in the clinical trials for such medicines, which could make it more difficult for us to complete enrollment for these clinical trials.

Certain of our medicines may compete with our other medicines, which could reduce our expected revenues.

Certain of our medicines inhibit the production of the same protein. For example, WAYLIVRA inhibits the production of the same protein as IONIS-APOCIII-L_{Rx} and TEGSEDI inhibits the production of the same protein as IONIS-TTR-L_{Rx}. We believe the enhancements we incorporated into IONIS-APOCIII-L_{Rx} and IONIS-TTR-L_{Rx} can provide greater patient convenience by allowing for significantly lower doses and less frequent administration compared to WAYLIVRA and TEGSEDI, respectively. As such, to the extent physicians and patients elect to use IONIS-APOCIII-L_{Rx} or IONIS-TTR-L_{Rx} instead of WAYLIVRA or TEGSEDI, respectively, it will reduce the revenue we derive from those medicines. In addition, while vupanorsen, IONIS-APOCIII-L_{Rx} and WAYLIVRA use different mechanisms of action, if vupanorsen and IONIS-APOCIII-L_{Rx} can effectively lower triglyceride levels in patients, including patients with FCS, WAYLIVRA, vupanorsen and IONIS-APOCIII-L_{Rx} may compete with each other.

Our medicines could be subject to regulatory limitations following approval.

Following approval of a medicine, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of medicines. Promotional communications regarding prescription medicines must be consistent with the information in the product's approved labeling. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development.

The FDA and foreign regulatory bodies have the authority to impose significant restrictions on an approved medicine through the product label and on advertising, promotional and distribution activities. For example:

- in the U.S., TEGSEDI's label contains a boxed warning for thrombocytopenia and glomerulonephritis;
- TEGSEDI requires periodic blood and urine monitoring;
- in the U.S., TEGSEDI is available only through a REMS program; and
- we expect WAYLIVRA will require periodic blood monitoring if approved in the U.S.

Prescription medicines may be promoted only for the approved indications in accordance with the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label may be subject to significant liability.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. For example, in connection with the conditional marketing approval for WAYLIVRA in the EU, we are required to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. If the results of such post-marketing studies are not satisfactory, the FDA, EC or other foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and time consuming to fulfill.

If we or others identify side effects after any of our medicines are on the market, or if manufacturing problems occur subsequent to regulatory approval, or if we, our manufacturers or our partners fail to comply with regulatory requirements, we or our partners may, among other things, lose regulatory approval and be forced to withdraw products from the market, need to conduct additional clinical studies, incur restrictions on the marketing, distribution or manufacturing of the product, and/or change the labeling of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA.

We depend on our collaboration with Biogen for the development and commercialization of SPINRAZA.

We have entered into a collaborative arrangement with Biogen to develop and commercialize SPINRAZA. We entered into this collaboration primarily to:

- fund our development activities for SPINRAZA;
- seek and obtain regulatory approvals for SPINRAZA; and
- successfully commercialize SPINRAZA.

We are relying on Biogen to obtain additional regulatory approvals for SPINRAZA, manufacture and successfully commercialize SPINRAZA. In general, we cannot control the amount and timing of resources that Biogen devotes to our collaboration. If Biogen fails to further develop SPINRAZA, obtain additional regulatory approvals for SPINRAZA, manufacture or commercialize SPINRAZA, or if Biogen's efforts are not effective, our business may be negatively affected.

Our collaboration with Biogen may not continue for various reasons. Biogen can terminate our collaboration at any time. If Biogen stops developing or commercializing SPINRAZA, we would have to seek or spend additional funding, and SPINRAZA's commercialization may be harmed or delayed.

Our collaboration with Biogen may not result in the continued successful commercialization of SPINRAZA. If Biogen does not continue to successfully commercialize SPINRAZA, we will receive limited revenues for SPINRAZA.

If we cannot optimize and maintain effective marketing and sales capabilities or enter into agreements with third parties to market and sell TEGSEDI and WAYLIVRA, we may not generate significant product revenue from TEGSEDI or WAYLIVRA.

To successfully commercialize TEGSEDI and WAYLIVRA, we must effectively manage our marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. We may not be successful in doing so. To commercialize WAYLIVRA in the initial indications we are pursuing and to continue the commercialization of TEGSEDI, we will need to optimize and maintain specialty sales forces in the global regions where we currently market or expect to market TEGSEDI and WAYLIVRA, supported by case managers, reimbursement specialists, partnerships with specialty pharmacies, injection training, routine blood and urine monitoring and a medical affairs team.

Even though certain members of our management team and other employees have experience commercializing medicines, as a whole we have limited experience marketing, selling and distributing medicines, and there are significant risks involved in building, tailoring, optimizing and managing a commercial infrastructure. We expect the recent Akcea Acquisition will result in significant turnover that could impair our ability to manage Akcea's business. If our efforts to integrate key Akcea employees into Ionis following the Akcea Acquisition are not successful, it could impair our ability to commercialize TEGSEDI and WAYLIVRA.

It is expensive and time consuming for us to maintain our own sales forces and related compliance protocols to market TEGSEDI and WAYLIVRA. We may never successfully optimize or manage this capability and any failure could harm the commercial launch of WAYLIVRA or adversely affect TEGSEDI sales. Additionally, we and our partners will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel.

We have incurred expenses launching, optimizing and managing the marketing and sales infrastructure for TEGSEDI in Europe, Canada and the U.S., and WAYLIVRA in Europe. If regulatory requirements or other factors cause the commercialization of TEGSEDI or WAYLIVRA to be less successful than expected in important markets, we would incur additional expenses for having invested in these capabilities prior to realizing any significant revenue from sales of TEGSEDI or WAYLIVRA. Our sales force and marketing teams may not successfully commercialize TEGSEDI or WAYLIVRA.

To the extent we decide to rely on third parties to commercialize TEGSEDI or WAYLIVRA in a particular geographic market, we will have less control over sales efforts and may receive less revenue than if we commercialized TEGSEDI or WAYLIVRA by ourselves. We have entered into agreements with third parties to commercialize our medicines as follows:

- In December 2020, we entered into a distribution agreement with Sobi to commercialize TEGSEDI and WAYLIVRA in Europe;
- In August 2018, we granted PTC the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries; and
- In August 2018 we entered into an agreement with Accredo Health Group, Inc., or Accredo, a subsidiary of Express Scripts, to be our specialty pharmacy partner for distribution of TEGSEDI in the U.S.

If Sobi or PTC does not successfully commercialize TEGSEDI or WAYLIVRA, including as a result of delays or disruption caused by the current COVID-19 Pandemic, we may receive limited revenue for TEGSEDI or WAYLIVRA in Europe, Latin America or certain Caribbean countries.

If we cannot effectively build and manage our distribution, medical affairs, market access, marketing and sales infrastructure, or find a suitable third party to perform such functions, the sales of TEGSEDI and WAYLIVRA may be adversely affected. Any such events may result in decreased sales and lower revenue, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

In addition, in response to the public health directives and orders related to the COVID-19 Pandemic, we implemented work-from-home policies for our employees globally and suspended business-related travel. We believe the effects of the government orders and our work-from-home and travel policies in response to the COVID-19 Pandemic have thus far had a limited impact on our productivity, business and commercialization efforts for TEGSEDI and WAYLIVRA, but the effects of these orders and policies may become more significant in the future.

Our operations are subject to additional healthcare laws.

Our operations are subject to additional healthcare laws, including federal and state anti-kickback laws, false claims laws, transparency laws, such as the federal Sunshine Act, and health information privacy and security laws. Efforts to ensure that our operations comply with applicable healthcare laws and regulations involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. Penalties for violations of applicable healthcare laws and regulations may include significant civil, criminal and administrative penalties, damages, disgorgement, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and additional reporting requirements and oversight if we enter into a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws. In addition, violations may also result in reputational harm, diminished profits and future earnings.

If government or other third-party payers fail to provide adequate coverage and payment rates for our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, our revenue will be limited.

In both domestic and foreign markets, sales of our current and future products will depend in part upon the availability of coverage and reimbursement from third-party payers. The majority of patients in the U.S. who would fit within our target patient populations for our medicines have their healthcare supported by a combination of Medicare coverage, other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new medicines when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be enough to make our medicines affordable. Accordingly, SPINRAZA, TEGSEDI and WAYLIVRA for FCS in the EU and, if approved, WAYLIVRA in the U.S. or Canada and for additional indications, and our medicines in development, will face competition from other therapies and medicines for limited financial resources. We or our partners may need to conduct post-marketing studies to demonstrate the cost-effectiveness of any future products to satisfy third-party payers. These studies might require us to commit a significant amount of management time and financial and other resources. Third-party payers may never consider our future products as cost-effective. Adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Third-party payers, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the U.S., no uniform policy of coverage and reimbursement for medicines exists among third-party payers. Therefore, coverage and reimbursement for medicines can differ significantly from payer to payer. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the Affordable Care Act, was passed in March 2010, and substantially changed the way healthcare is financed by both governmental and private insurers, and continues to significantly impact the U.S. pharmaceutical industry. There remain judicial and Congressional challenges to certain aspects of the Affordable Care Act, as well as efforts to repeal or replace certain aspects of the Affordable Care Act. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the Affordable Care Act are invalid as well. However, in March 2020, before the District Court could rule on the remaining provisions of the Affordable Care Act, the U.S. Supreme Court agreed to review the case. In November 2020, the U.S. Supreme Court heard oral arguments and is expected to rule on the case in its current session, which began in October 2020. Although the U.S. Supreme Court has not yet ruled on the constitutionality of the Affordable Care Act, on January 28, 2021, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace. It is unclear how the Supreme Court ruling, other such litigation and healthcare reform measures will impact the Affordable Care Act and our business.

Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the U.S. and in international markets. For example, in the U.S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U.S. Congressional inquiries and legislation designed to, among other things, reform government program reimbursement methodologies for medicines and bring more transparency to drug pricing. Such restrictions may include legislative proposals seeking to reduce drug prices (e.g., by placing limits on pharmaceutical price increases and tying Medicare Part B drug prices to international drug prices), increase competition (e.g., by allowing for personal importation of drugs from Canada), lower out-of-pocket drug costs for patients (e.g., by capping Medicare Part D beneficiary out-of-pocket pharmacy expenses) and increase patient access to lower-cost generic and biosimilar drugs. In November 2020, the U.S. Department of Health and Human Services issued a final rule modifying the anti-kickback law safe harbors for plans, pharmacies, and pharmaceutical benefit managers. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Third-party coverage and reimbursement for medicines may not be available or adequate in either the U.S. or international markets, and third-party payers, whether foreign or domestic, or governmental or commercial, may allocate their resources to address the current COVID-19 Pandemic or experience delays or disruptions in their ability to devote resources to coverage and reimbursement matters related to our products or medicines as a result of the COVID-19 Pandemic, which would negatively affect the potential commercial success of our products, our revenue and our profits.

If we cannot manufacture our medicines or contract with a third party to manufacture our medicines at costs that allow us to charge competitive prices to buyers, we cannot market our products profitably.

To successfully commercialize any of our medicines, we would need to optimize and manage large-scale commercial manufacturing capabilities either on a standalone basis or through a third-party manufacturer. We rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and drug product for WAYLIVRA. Any delays or disruption to our own or third-party commercial manufacturing capabilities, including any interruption to our supply chain as a result of the current COVID-19 Pandemic, could limit the commercial success of our medicines.

In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our medicines, called oligonucleotides, on a commercial scale for the systemic administration of a medicine. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our medicines, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our drug costs. We or our partners may not be able to manufacture our medicines at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's cGMP regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We, our partners and our contract manufacturers may not comply or maintain compliance with cGMP, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing authorizations for our medicines, including authorizations for SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, or result in enforcement action after authorization that could limit the commercial success of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development.

Risks Related to the Development and Regulatory Approval of our Medicines

If we or our partners fail to obtain regulatory approval for our medicines and additional approvals for SPINRAZA, TEGSEDI and WAYLIVRA, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our medicines will be considered safe and effective or will be approved for commercialization. In addition, it is possible that SPINRAZA, TEGSEDI and WAYLIVRA may not be approved in additional markets or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to demonstrate the safety and efficacy of each of our medicines before they can be approved or receive additional approvals for sale. We and our partners must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for our medicines. It is possible that regulatory agencies will not approve our medicines for marketing or SPINRAZA, TEGSEDI or WAYLIVRA in additional markets or for additional indications. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or our medicines in development, the agency will not approve the specific medicine or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the medicine. For example, in August 2018 we received a complete response letter from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Non-W from Health Canada for WAYLIVRA in November 2018. We are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA.

The FDA or other comparable foreign regulatory authorities can delay, limit or deny approval of a medicine for many reasons, including:

- such authorities may disagree with the design or implementation of our clinical studies;
- we or our partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a medicine is safe and effective for any indication;
- such authorities may not accept clinical data from studies conducted at clinical facilities that have deficient clinical practices or that are in countries where the standard of care is potentially different from the U.S.;
- we or our partners may be unable to demonstrate that our medicine's clinical and other benefits outweigh its safety risks to support approval;
- such authorities may disagree with the interpretation of data from preclinical or clinical studies;
- such authorities may find deficiencies in our manufacturing processes or facilities or those of third-party manufacturers who manufacture clinical and commercial supplies for our medicines, or may delay the inspection of such facilities due to restrictions related to the COVID-19 Pandemic; and
- the approval policies or regulations of such authorities or their prior guidance to us or our partners during clinical development may significantly change in a manner rendering our clinical data insufficient for approval.

Failure to receive marketing authorization for our medicines, or failure to receive additional marketing authorizations for SPINRAZA, TEGSEDI or WAYLIVRA, or delays in these authorizations could prevent or delay commercial introduction of the medicine, and, as a result, could negatively impact our ability to generate revenue from product sales.

If the results of clinical testing indicate that any of our medicines are not suitable for commercial use, we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense medicines are a relatively new approach to therapeutics. If we cannot demonstrate that our medicines are safe and effective for human use in the intended indication, we may need to abandon one or more of our drug development programs.

In the past, we have invested in clinical studies of medicines that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur in clinical studies for our medicines, including the studies of tominersen, tofersen, pelacarsen, IONIS-TTR-L_{Rx} and IONIS-APOCIII-L_{Rx}. If any of our medicines in clinical studies, including tominersen, tofersen, pelacarsen, IONIS-TTR-L_{Rx} and IONIS-APOCIII-L_{Rx}, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

Even if our medicines are successful in preclinical and human clinical studies, the medicines may not be successful in late-stage clinical studies.

Successful results in preclinical or initial human clinical studies, including the Phase 2 results for some of our medicines in development, may not predict the results of subsequent clinical studies, including the studies of tominersen, tofersen, pelacarsen, IONIS-TTR-L_{Rx} and IONIS-APOCIII-L_{Rx}. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a medicine on subjects in the trial;
- we, or our partners, may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- enrollment in our clinical studies may be slower than we anticipate;
- we or our partners, including our independent clinical investigators, contract research organizations and other third-party service providers on which we rely, may not identify, recruit and train suitable clinical investigators at a sufficient number of study sites or timely enroll a sufficient number of study subjects in the clinical study;
- the institutional review board for a prospective site might withhold or delay its approval for the study;
- enrollment in our clinical studies may be slower than we anticipate;
- people who enroll in the clinical study may later drop out due to adverse events, a perception they are not benefiting from participating in the study, fatigue with the clinical study process or personal issues;
- a clinical study site may deviate from the protocol for the study;
- the cost of our clinical studies may be greater than we anticipate;
- our partners may decide not to exercise any existing options to license and conduct additional clinical studies for our medicines; and
- the supply or quality of our medicines or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

The current COVID-19 Pandemic could make some of these factors more likely to occur.

In addition, our current medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could have, or be perceived by a regulatory authority to have, an impact on a different medicine we are developing. This could cause the FDA and other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our medicines or increase our costs. For example, the FDA or other regulatory agencies could request,

among other things, any of the following regarding one of our medicines: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. This happened in connection with the conditional marketing approval for WAYLIVRA in the EU, as the EC is requiring us to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. We have an ongoing OLE extension study of WAYLIVRA in patients with FCS and an OLE study of TEGSEDI in patients with hATTR, and an early access program, or EAP, for WAYLIVRA. Adverse events or results from these studies or the EAPs could negatively impact our pending or future marketing approval applications for WAYLIVRA and TEGSEDI in patients with FCS or hATTR amyloidosis or the commercial opportunity for WAYLIVRA or TEGSEDI.

Any failure or delay in the clinical studies, including the studies of tominersen, tofersen, pelacarsen, IONIS-TTR-L_{Rx} and IONIS-APOCIII-L_{Rx}, could reduce the commercial potential or viability of our medicines.

We depend on third parties to conduct our clinical studies for our medicines and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our medicines and expect to continue to do so in the future. For example, we use clinical research organizations, such as Pharmaceutical Research Associates, Inc., Icon Clinical Research Limited, Syneos Health, Inc., PPD and Medpace for the clinical studies for our medicines, including tominersen, tofersen, pelacarsen, IONIS-TTR-L_{Rx} and IONIS-APOCIII-L_{Rx}. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations, including as a result of delays or disruption caused by the current COVID-19 Pandemic that may affect the third party's ability to conduct the clinical studies for our medicines, or a termination of our relationship with these third parties could delay or prevent the development, marketing authorization and commercialization of our medicines or additional marketing authorizations for TEGSEDI and WAYLIVRA.

Since corporate partnering is a significant part of our strategy to fund the advancement and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, or if we cannot obtain additional partners, we may have to delay or stop progress on our drug development programs.

To date, corporate partnering has played a significant role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize many of our unpartnered medicines. However, we may not be able to negotiate favorable collaborative arrangements for these drug programs. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our medicines could suffer.

Our corporate partners are developing and/or funding many of the medicines in our development pipeline. For example, we are relying on:

- Roche for development and funding of tominersen;
- Novartis for development and funding of pelacarsen; and
- Biogen for development and funding of tofersen.

If any of these pharmaceutical companies stops developing and/or funding these medicines, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these medicines on our own. Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. For example, as part of a reprioritization of its pipeline and strategic review of its rare disease business, GSK declined its option to license TEGSEDI and IONIS-FB-L_{Rx}.

Even with funding from corporate partners, if our partners do not effectively perform their obligations under our agreements with them, it would delay or stop the progress of our drug development and commercial programs.

In addition to receiving funding, we enter into collaborative arrangements with third parties to:

- conduct clinical studies;
- seek and obtain marketing authorization; and
- manufacture, market and sell our medicines.

Once we have secured a collaborative arrangement to further develop and commercialize one of our drug development programs, such as our collaborations with AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis, Pfizer and Roche, these collaborations may not continue or result in commercialized medicines, or may not progress as quickly as we first anticipated.

For example, a collaborator such as AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis, Pfizer or Roche, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the medicine that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our medicines than it does for its own medicines.

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our medicines, including SPINRAZA, tominersen, pelacarsen and tofersen.

If we do not progress in our programs as anticipated, the price of our securities could decrease.

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain medicine will enter clinical trials, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, marketing authorization, or when we or our partners plan to commercially launch a medicine. We base our estimates on present facts and a variety of assumptions, many of which are outside of our control, including the current COVID-19 Pandemic. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to SPINRAZA, TEGSEDI, WAYLIVRA, tominersen, tofersen, pelacarsen, IONIS-TTR-L_{Rx} and IONIS-APOCIII-L_{Rx}, the price of our securities could decrease.

Risks Associated with our Businesses as a Whole

Risks related to our financial results

We have incurred losses, and our business will suffer if we fail to consistently achieve profitability in the future.

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of December 31, 2020, we had an accumulated deficit of approximately \$1.2 billion and stockholders' equity of approximately \$0.8 billion. Most of our historical losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our income has come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from the sale or licensing of our patents, as well as interest income. If we do not continue to earn substantial revenue, we may incur additional operating losses in the future. We may not successfully develop any additional products or achieve or sustain future profitability.

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.

Many of our medicines are undergoing clinical studies or are in the early stages of research and development. Most of our drug programs will require significant additional research, development, manufacturing, preclinical and clinical testing, marketing authorization, preclinical activities and commitment of significant additional resources

prior to their successful commercialization. These activities will require significant cash. As of December 31, 2020, we had cash, cash equivalents and short-term investments equal to \$1.9 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or to license certain medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- successful commercialization of SPINRAZA, TEGSEDI and WAYLIVRA;
- additional marketing approvals for WAYLIVRA and TEGSEDI;
- the profile and launch timing of our medicines, including TEGSEDI and WAYLIVRA;
- the results of the clinical studies of tominersen, tofersen, pelacarsen, IONIS-TTR-L_{Rx} and IONIS-APOCIII-L_{Rx};
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining marketing authorizations; and
- competing technological and market developments, including the introduction by others of new therapies that address our markets.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and the price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies or medicines.

Risks related to our intellectual property

If we cannot protect our patent rights or our other proprietary rights, others may compete more effectively against us.

Our success depends to a significant degree upon whether we can continue to develop, secure and maintain intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the U.S. or in other countries and we may not be able to obtain, maintain or enforce our patents and other intellectual property rights which could impact our ability to compete effectively. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, other parties may successfully challenge, invalidate or circumvent our issued patents or patents licensed to us so that our patent rights do not create an effective competitive barrier or revenue source.

We cannot be certain that the U.S. Patent and Trademark Office, or U.S. PTO, and courts in the U.S. or the patent offices and courts in foreign countries will consider the claims in our patents and applications covering SPINRAZA, TEGSEDI, WAYLIVRA, or any of our medicines in development as patentable. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent, including through legal action.

If we or any licensor partner loses or cannot obtain patent protection for SPINRAZA, TEGSEDI, WAYLIVRA, or any of our other medicines in development, it could have a material adverse impact on our business.

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

From time to time we have to defend our intellectual property rights. If we are involved in an intellectual property dispute, we may need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the U.S. PTO or the International Trade Commission or foreign patent authorities. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

If a third-party claims that our medicines or technology infringe its patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the U.S. are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain.

Risks related to our business strategy and personnel

If we fail to successfully integrate Akcea’s business and operations, it may adversely affect our future results.

We believe our Akcea Acquisition will result in certain benefits, including a single vision and set of strategic priorities, led by one team, accelerating our next phase of growth and positioning us to more effectively deliver our medicines to patients. Under this transaction, Ionis will now retain more value from Akcea’s pipeline and commercial products, further strengthening our financial position and supporting continued investments in our future. The success of the transaction will depend on our ability to realize these anticipated benefits. We may fail to realize the anticipated benefits of the Akcea Acquisition for a variety of reasons, including the following:

- failure to successfully manage relationships with partners, customers, distributors and suppliers;
- disruptions to Akcea’s commercial operations;
- potential incompatibility of technologies and systems;
- failure to leverage the capabilities of the combined company quickly and effectively;
- potential difficulties integrating and harmonizing business systems and processes;
- tax benefits of the combined structure may not be available or in the expected amounts; and
- the loss of key employees.

If our management transition is not successful our business could suffer.

In January 2020, Dr. Croke, our founder and Chief Executive Officer, transitioned from Chief Executive Officer to Executive Chairman of our Board of Directors. As Executive Chairman, Dr. Croke continues to be responsible for the activities of the board and remains active in the company, providing strategic advice and continuing to participate in the scientific activities. Starting in January 2020, Dr. Monia, who had been our Chief Operating Officer from January 2018 to January 2020 and has been a member of our team since our founding over 30 years ago, serves as our Chief Executive Officer. Following our 2021 Annual Meeting of Stockholders in June, Dr. Croke will retire from Ionis and its board of directors but will continue to serve as a scientific advisor. If this transition is not successful, our business could suffer.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers that would prevent them from leaving us. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development

work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies may make it more challenging to recruit and retain qualified scientific personnel. Similarly, if we cannot recruit and retain qualified marketing, sales and distribution personnel, our ability to effectively implement our new commercial strategy following the Akcea Acquisition will be adversely affected.

Risks related to taxes

Our ability to use our net operating loss carryovers and certain other tax attributes may be limited.

Under the Internal Revenue Code of 1986, as amended, or the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year. Under that provision, we can carryforward our NOLs to offset our future taxable income, if any, until such NOLs are used or expire. The same is true of other unused tax attributes, such as tax credits.

Under the Tax Cut and Jobs Act of 2017, or the Tax Act, as modified by the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, U.S. federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such U.S. federal net operating losses is limited to 80 percent of taxable income beginning in 2021. It is uncertain if and to what extent various states will conform to the federal Tax Act or the CARES Act. The CARES Act also reinstated the net operating loss carryback provisions whereby net operating losses incurred in calendar tax years 2018, 2019 and 2020 may be carried back to offset taxable income of the five tax years preceding the year of the loss.

At the state level, there may be periods during which the use of net operating losses is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed. For example, in June 2020, California enacted Assembly Bill 85 (AB 85), which suspends NOLs and limits credit utilization to \$5 million per year for the 2020, 2021 and 2022 tax years. AB 85 did not have a material impact on our 2020 tax provision, but it is possible that it may in future years.

In addition, under Sections 382 and 383 of the Code, and corresponding provisions of state law, if a corporation undergoes an “ownership change,” which is generally defined as a greater than 50 percent change, by value, in its equity ownership over a three-year period, the corporation’s ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our net operating loss carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. As a result of the Akcea Acquisition, we will be subject to the Separate Return Limitation Year, or SRLY, Rules. Under SRLY, our utilization of Akcea’s pre-acquisition net operating loss and tax credit carryforwards will be limited to the amount of income that Akcea contributes to our consolidated taxable income. The Akcea pre-acquisition tax attributes cannot be used to offset any of the income that Ionis contributes to our consolidated taxable income.

We have assessed our valuation allowances requirements, both federal and state, due to the Akcea Acquisition, and have also assessed whether Akcea may rejoin our consolidated tax group. For details regarding these assessments, see Note 5, *Income Taxes*, in the Notes to the Consolidated Financial Statements.

Our future taxable income could be impacted by changes in tax laws, regulations and treaties.

A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us.

We could be subject to additional tax liabilities.

We are subject to U.S. federal, state, local and sales taxes in the U.S. and foreign income taxes, withholding taxes and transaction taxes in foreign jurisdictions. Significant judgment is required in evaluating our tax positions and our worldwide provision for taxes. During the ordinary course of business, there are many activities and transactions for which the ultimate tax determination is uncertain. In addition, our tax obligations and effective tax rates could be adversely affected by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations, including those relating to income tax nexus, by recognizing tax losses or lower than anticipated

earnings in jurisdictions where we have lower statutory rates and higher than anticipated earnings in jurisdictions where we have higher statutory rates, by changes in foreign currency exchange rates, or by changes in the valuation of our deferred tax assets and liabilities. We may be audited in various jurisdictions, and such jurisdictions may assess additional taxes, sales taxes and value-added taxes against us. Although we believe our tax estimates are reasonable, the final determination of any tax audits or litigation could be materially different from our historical tax provisions and accruals, which could have a material adverse effect on our operating results or cash flows in the period for which a determination is made.

General risk factors

If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding December 31, 2020, the market price of our common stock ranged from \$64.34 to \$39.32 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, the commercial success of our approved medicines, governmental regulation, marketing authorizations, changes in payers' reimbursement policies, developments in patent or other proprietary rights and public concern regarding the safety of our medicines.

The current COVID-19 Pandemic has caused a significant disruption of global financial markets and has resulted in increased volatility in the trading price of our common stock. Additionally, broad market and industry factors may also materially harm the market price of our common stock irrespective of our operating performance. The stock market in general, and NASDAQ and the market for biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the particular companies affected. The trading prices and valuations of these stocks, and of ours, may not be predictable. A loss of investor confidence in the market for biotechnology or pharmaceutical stocks or the stocks of other companies which investors perceive to be similar to us, the opportunities in the biotechnology and pharmaceutical market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations.

Provisions in our certificate of incorporation, convertible notes documents, call spread hedge transaction documents and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66 2/3 percent of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We have in the past, and may in the future, implement a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. In addition, our board of directors has the authority to fix the rights and preferences of, and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

The provisions of our convertible senior notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange \$375.6 million of our 1% Notes for

\$439.3 million of our 0.125% Notes, and to issue \$109.5 million of our 0.125% Notes. Additionally, in connection with the pricing of our 0.125% Notes, we entered into call spread transactions in which we purchased note hedges and sold warrants. Terminating or unwinding the call spread transactions could require us to make substantial payments to the counterparties under those agreements or may increase our stock price. The costs or any increase in stock price that may arise from terminating or unwinding such agreements could make an acquisition of our company significantly more expensive to the purchaser.

These provisions, as well as Delaware law, including Section 203 of the Delaware General Corporation Law, and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests.

Future sales of our common stock in the public market could adversely affect the trading price of our securities.

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 11.2 million shares of our common stock upon conversion of our convertible senior notes and up to 6.6 million shares may be issued in connection with the warrant transactions we entered into in connection with the issuance of our 0.125% Notes, in each case subject to customary anti-dilution adjustments. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

In addition, pursuant to the call spread transactions we entered into in connection with the pricing of our 0.125% Notes, the counterparties are likely to modify their hedge positions from time to time at or prior to the conversion or maturity of the notes by purchasing and selling shares of our common stock, other of our securities, or other instruments, including over-the-counter derivative instruments, that they may wish to use in connection with such hedging, which may have a negative effect on the conversion value of those notes and an adverse impact on the trading price of our common stock. The call spread transactions are expected generally to reduce potential dilution to holders of our common stock upon any conversion of our 0.125% Notes or offset any cash payments we are required to make in excess of the principal amount of the converted 0.125% Notes, as the case may be. However, the warrant transactions could separately have a dilutive effect to the extent that the market value per share of our common stock exceeds the applicable strike price of the warrants.

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, product liability claims may result in decreased demand for our medicines, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material.

We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks.

We are dependent upon our own and third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity, with third-party phishing and social engineering attacks in particular increasing in connection with the COVID-19 Pandemic. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their

systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and state breach notification laws and foreign law equivalents, subject us to financial penalties and mandatory and costly corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, our efforts may not prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

Because we use biological materials, hazardous materials, chemicals and radioactive compounds, 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 activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We store most of these materials and various wastes resulting from their use at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance in amounts and types that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research, development or manufacturing efforts caused by contamination, and the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

If a natural or man-made disaster strikes our research, development or manufacturing facilities or otherwise affects our business, it could delay our progress developing and commercializing our medicines.

We manufacture most of our research and clinical supplies in a manufacturing facility located in Carlsbad, California. We manufacture the finished drug product for TEGSEDI and WAYLIVRA at third-party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA. The facilities and the equipment we, our partners and our contract manufacturers use to research, develop and manufacture our medicines would be costly to replace and could require substantial lead time to repair or replace. Our facilities or those of our partners or contract manufacturers may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires, acts of terrorism and pandemics; and if such facilities are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess property damage and business interruption insurance coverage, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the U.S. government, including the FDA.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we continue to incur additional expenses and divert our management's time

to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock.

The SEC and other regulators have continued to adopt new rules and regulations and make additional changes to existing regulations that require our compliance. On July 21, 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation-related provisions in the Dodd-Frank Act that require the SEC to adopt, or where the SEC has adopted, additional rules and regulations in these areas such as “say on pay” and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business.

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole are currently experiencing substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government in response to the COVID-19 Pandemic. In the past, the failure, bankruptcy, or sale of various financial and other institutions created similar turmoil and uncertainty in such markets and industries. It is possible that a crisis in the global credit markets, the U.S. capital markets, the financial services industry or the U.S. economy may adversely affect our business, vendors and prospects, as well as our liquidity and financial condition. More specifically, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

A variety of risks associated with operating our business and marketing our medicines internationally could adversely affect our business.

In addition to our U.S. operations, we are commercializing TEGSEDI in the EU and Canada, and WAYLIVRA in the EU. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. Because we have international operations we are subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for our medicines and foreign employees;
- complexities associated with managing multiple payer reimbursement regimes, government payers or patient self-pay systems;
- difficulties in staffing and managing foreign operations;
- in certain circumstances, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA, and its equivalent in foreign jurisdictions;
- economic weakness, including inflation, natural disasters, war, events of terrorism, political instability or public health issues or pandemics, such as the current COVID-19 Pandemic, in particular foreign countries or globally;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenue, and other obligations related to doing business in another country;
- compliance with tax, employment, privacy, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.; and
- changes in diplomatic and trade relationships.

The United Kingdom's exit from the E.U. could increase these risks.

Our business activities outside of the U.S. are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom's Bribery Act 2010. In many other countries, the healthcare providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. There is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have an adverse impact on our business and financial condition.

The impact on us of the vote by the United Kingdom to leave the European Union cannot be predicted.

The withdrawal of the UK from the EU, commonly referred to as "Brexit," may adversely impact our ability to obtain regulatory approvals of our medicines in the EU, result in restrictions or imposition of taxes and duties for importing our medicines into the EU, and may require us to incur additional expenses in order to develop, manufacture and commercialize our medicines in the EU.

Following the result of a referendum in 2016, the UK left the EU on January 31, 2020. Pursuant to the formal withdrawal arrangements agreed between the UK and the EU, the UK was subject to a transition period that ended December 31, 2020, or the Transition Period, during which EU rules continued to apply. A trade and cooperation agreement, or the Trade and Cooperation Agreement, that outlines the future trading relationship between the UK and the EU was agreed in December 2020.

Since a significant proportion of the regulatory framework in the UK applicable to our business and our medicines is derived from EU directives and regulations, Brexit has had, and may continue to have, a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our medicines in the UK or the EU. For example, Great Britain is no longer covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA and, a separate marketing authorization will be required to market our medicines in Great Britain. It is currently unclear whether the Medicines & Healthcare products Regulatory Agency in the UK is sufficiently prepared to handle the increased volume of marketing authorization applications that it is likely to receive. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would delay or prevent us from commercializing our medicines in the UK or the EU.

While the Trade and Cooperation Agreement provides for the tariff-free trade of medicinal products between the UK and the EU, there may be additional non-tariff costs to such trade which did not exist prior to the end of the Transition Period. Further, should the UK diverge from the EU from a regulatory perspective in relation to medicinal products, tariffs could be put into place in the future. We could therefore, both now and in the future, face significant additional expenses (when compared to the position prior to the end of the Transition Period) to operate our business.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 18, 2021, the following are the primary facilities in which we operate:

<u>Property Description</u>	<u>Location</u>	<u>Square Footage</u>	<u>Owned or Leased</u>	<u>Initial Lease Term End Date</u>	<u>Lease Extension Options</u>
Laboratory and office space facility	Carlsbad, CA	176,000	Owned		
Office and meeting space facility	Carlsbad, CA	74,000	Owned		
Office space facility	Boston, MA	30,175	Leased	2028	One, five-year option to extend
Manufacturing facility	Carlsbad, CA	26,800	Owned		
Manufacturing support facility	Carlsbad, CA	25,800	Leased	2026	One, five-year option to extend
Office and storage space facility	Carlsbad, CA	18,700	Leased	2023	One, five-year option to extend
Office space facility	Carlsbad, CA	5,800	Leased	2023	One, five-year option to extend
		357,275			

Item 3. Legal Proceedings

For details of legal proceedings, see Note 9, *Legal Proceedings*, in the Notes to the Consolidated Financial Statements.

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 and Dividends**

Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol “IONS.” As of February 18, 2021, there were approximately 506 stockholders 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 stockholders represented by these record holders.

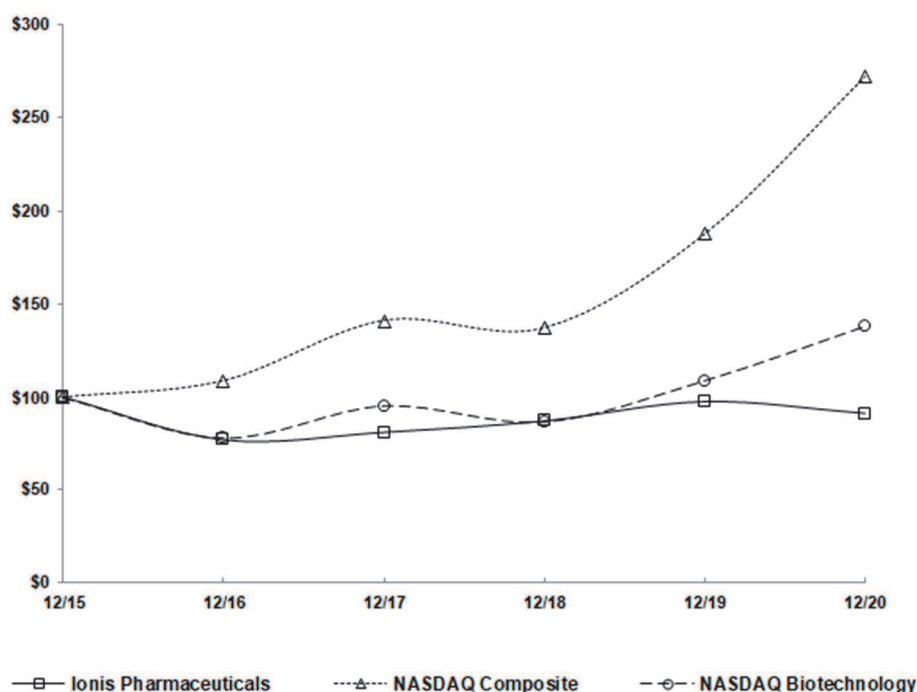
We have never paid dividends and do not anticipate paying any dividends in the foreseeable future.

Performance Graph⁽¹⁾

Set forth below is a table and chart comparing the total return on an indexed basis of \$100 invested on December 31, 2015 in our common stock, the Nasdaq Composite Index (total return) and the Nasdaq Biotechnology Index. The total return assumes reinvestment of dividends.

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN

Among Ionis Pharmaceuticals, the NASDAQ Composite Index
and the NASDAQ Biotechnology Index



* \$100 invested on December 31, 2015 in stock or index, including reinvestment of dividends. Fiscal year ending December 31.

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN

Among Ionis Pharmaceuticals, Inc., the Nasdaq Composite Index,
and the Nasdaq Biotechnology Index

	<u>Dec-15</u>	<u>Dec-16</u>	<u>Dec-17</u>	<u>Dec-18</u>	<u>Dec-19</u>	<u>Dec-20</u>
Ionis Pharmaceuticals, Inc.	\$100.00	\$ 77.23	\$ 81.22	\$ 87.29	\$ 97.55	\$ 91.30
Nasdaq Composite Index.	\$100.00	\$108.87	\$141.13	\$137.12	\$187.44	\$271.64
Nasdaq Biotechnology Index.	\$100.00	\$ 78.65	\$ 95.67	\$ 87.19	\$109.08	\$137.90

(1) This section is not “soliciting material,” is not deemed “filed” with the SEC, is not subject to the liabilities of Section 18 of the Exchange Act and is not to be incorporated by reference in any of our filings under the Securities Act or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

Item 6. Selected Financial Data

Refer to our financial data contained within Item 7, *Management’s Discussion and Analysis*, our financial statements and within other parts of this document.

Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations

This financial review presents our operating results for each of the two years in the period ended December 31, 2020, and our financial condition at December 31, 2020. Refer to our 2019 Form 10-K for our results of operations for 2019 compared to 2018. Except for the historical information contained herein, the following discussion contains forward-looking statements that are subject to known and unknown risks, uncertainties and other factors that may cause our actual results to differ materially from those expressed or implied by such forward-looking statements. We discuss such risks, uncertainties and other factors throughout this report and specifically under Item 1A of Part I of this report, “Risk Factors.” In addition, the following review should be read in conjunction with the information presented in our consolidated financial statements and the related notes to our consolidated financial statements as indexed on page F-1.

Overview

As noted in our Business Overview in Part I of this report, for more than 30 years, we have been a leader in RNA-targeted therapy and believe our medicines are pioneering new markets, changing standards of care and transforming the lives of people with devastating diseases. We currently have three marketed medicines and a late-stage pipeline primarily focused on two core franchises: neurology and cardiometabolic. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming one of the most successful biotechnology companies. For further details on our business refer to the Business section of Part I of this report.

Financial Highlights

The following is a summary of our financial results (in millions):

	Year Ended December 31,	
	2020	2019
Total revenue	\$ 729.3	\$1,122.6
Total operating expenses	\$ 901.3	\$ 756.7
Income (loss) from operations.	\$ (172.1)	\$ 365.9
Net income (loss).	\$ (486.8)	\$ 303.3
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	\$ (451.3)	\$ 294.1
Cash, cash equivalents and short-term investments	\$1,892.4	\$2,499.5

Commercial revenue increased in 2020 compared to 2019 due to an increase in product sales from TEGSEDI and WAYLIVRA, primarily from major market launches in 2020. Our R&D revenue in 2019 was higher compared to 2020 primarily because of license fees we recognized in 2019. In 2019, we earned approximately \$400 million of revenue from licensing vupanorsen to Pfizer and pelacarsen to Novartis.

Our operating expenses for 2020 increased compared to 2019 principally due to our investments in the Phase 3 program for IONIS-TTR-L_{Rx} and our wholly owned pipeline. Additionally, we incurred approximately \$90 million in costs related to the Akcea Acquisition and restructured European operations. The costs primarily consisted of severance and retention costs of \$29 million and stock-based compensation expense for the acceleration of Akcea equity awards of \$59 million.

Our net loss for 2020 included income tax expense of \$317 million compared to \$44 million in 2019. The increase was primarily due to a non-cash tax expense of \$313 million related to an increase in the valuation allowance we recorded against our federal net deferred tax assets. As a result of the Akcea Acquisition, Ionis and Akcea will file their federal taxes on a consolidated basis beginning in the fourth quarter of 2020. We recorded a valuation allowance against all of Ionis’ federal net deferred tax assets in the fourth quarter of 2020, due largely to Akcea’s history of losses, and the expected impact of this on Ionis’ consolidated federal taxable income. We now maintain a valuation allowance against all our consolidated federal and state net deferred tax assets. See Note 5, *Income Taxes*, in the Notes to the Consolidated Financial Statements for further discussion on our valuation allowance assessment.

With \$1.9 billion in cash and short-term investments at December 31, 2020, we believe we have the financial resources to execute on our strategic priorities for 2021 and beyond.

Business Segments

Through 2020, we had two operating segments, our Ionis Core segment and Akcea Therapeutics. Akcea was focused on developing and commercializing medicines to treat patients with serious and rare diseases. We have provided segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviewed to assess operating performance and to make operating decisions through 2020. We allocated a portion of Ionis' development, R&D support and general and administrative expenses to Akcea for work Ionis performed on behalf of Akcea and we billed Akcea for these expenses. As a result of acquiring Akcea in the fourth quarter of 2020 we integrated Akcea operations within Ionis. Beginning in 2021, our chief decision maker began assessing operating performance and making operating decisions on a single segment basis, which we refer to as Ionis Pharmaceuticals.

Critical Accounting Estimates

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management reviews the development, selection and disclosure of such estimates with the audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting estimates and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment. Our significant accounting policies are outlined in Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements.

The following are our significant accounting estimates, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results:

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Estimating our income taxes.

The following are descriptions of our critical accounting estimates.

Revenue Recognition

We earn revenue from several sources. The judgements and estimates we make vary between each source of our revenue. The following is a summary of the critical accounting estimates we make with respect to each of our significant revenue sources.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We estimate our commercial revenue from SPINRAZA royalties based on reporting we receive from Biogen each quarter. We use this reporting to calculate our royalty revenue based on our tiered contractual royalty rate for the given period based on annual cumulative net sales. We record our royalty revenue in the same period in which Biogen sells SPINRAZA. We also estimate commercial revenue from licensing and other royalty revenue.

Commercial Revenue: Product sales, net

We added product sales from TEGSEDI to our commercial revenue in the fourth quarter of 2018 and we added product sales from WAYLIVRA to our commercial revenue in the third quarter of 2019. We recognize product sales in the period when our customer obtains control of our products. We record product sales at our net sales price, which includes estimated reserves for discounts, returns, chargebacks, rebates, co-pay assistance and other allowances that we offer under contracts between us and our customers, wholesalers, health care providers and other indirect customers. Actual amounts may vary from our estimates. Our historical reserve estimates have not been materially different from our actual amounts. The total reserves we estimated during 2020 and 2019 were not material to our financial results.

Research and development revenue under collaborative agreements

We recognize R&D revenue from numerous collaboration agreements. Our collaboration agreements typically contain multiple elements, or performance obligations, including technology licenses or options to obtain technology licenses, R&D services, and manufacturing services. Upon entering into a collaboration agreement, we are required to make the following judgements:

- Identifying the performance obligations contained in the agreement

Our assessment of what constitutes a separate performance obligation requires us to apply judgement. Specifically, we have to identify which goods and services we are required to provide under the contract are distinct.

- Determining the transaction price, including any variable consideration

To determine the transaction price, we review the amount of consideration we are eligible to earn under the agreement. We do not typically include any payments we may receive in the future in our initial transaction price since the payments are typically not probable because they are contingent upon certain future events.

We are required to reassess the total transaction price at each reporting period to determine if we should include additional payments in the transaction price that have become probable. For example, in the fourth quarter of 2020, we achieved a milestone payment for \$7.5 million under our 2018 strategic neurology collaboration with Biogen. Prior to achieving this milestone payment, we did not consider this payment probable. Upon achieving the milestone payment, we reassessed the total transaction price of our 2018 strategic neurology collaboration. We added this milestone payment to our total transaction price under our collaboration.

- Allocating the transaction price to each of our performance obligations

When we allocate the transaction price to more than one performance obligation, we make estimates of the relative stand-alone selling price of each performance obligation because we do not typically sell our goods or services on a stand-alone basis. The estimate of the relative stand-alone selling price requires us in some cases to make significant judgements. For example, when we deliver a license at the start of an agreement, we use valuation methodologies, such as the relief from royalty method, to value the license. Under this method we are required to make estimates including: future sales, royalties on future product sales, contractual milestones, expenses, income taxes and discount rates. Additionally, when we estimate the selling price for R&D services, we make estimates, including: the number of internal hours we will spend on the services, the cost of work we and third parties will perform and the cost of clinical trial material we will use.

The R&D revenue we recognize each period is comprised of several types of revenue, including amortization from upfront payments, milestone payments, license fees and other services. Each of these types of revenue require us to make various judgements and estimates.

Amortization from Upfront Payments

We recognize revenue from the amortization of upfront payments as we perform R&D services. We use an input method to estimate the amount of revenue to recognize each period. This method requires us to make estimates of the total costs we expect to incur to complete our R&D services performance obligation or the total length of time it will take us to complete our R&D services performance obligation. If we change our estimates, we may have to adjust our revenue. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion of the cumulative catch up adjustment we made.

Milestone Payments

When recognizing revenue related to milestone payments we typically make the following judgements and estimates:

- Whether the milestone payment is probable (discussed in detail above under “Determining the transaction price, including any variable consideration”); and
- Whether the milestone payment relates to services we are performing or if our partner is performing the services:

- If we are performing services, we recognize revenue over our estimated period of performance in a similar manner to the amortization of upfront payments (discussed above under “Amortization of Upfront payments”).
- Conversely, we recognize in full those milestone payments that we earn based on our partners’ activities when our partner achieves the milestone event and we do not have a performance obligation.

License Fees

When we grant a license for a medicine in clinical development, we generally recognize as R&D revenue the total amount we determine to be the relative stand-alone selling price of a license when we deliver the license to our partner. We discuss the estimates we make related to the relative stand-alone selling price of a license in detail above under “Allocating the transaction price to each of our performance obligations”.

Estimated Liability for Clinical Development Costs

We have numerous medicines in preclinical studies and/or clinical trials at clinical sites throughout the world. On at least a quarterly basis, we estimate our liability for preclinical and clinical development costs we have incurred and services that we have received but for which we have not yet been billed and maintain an accrual to cover these costs. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. We estimate our liability using assumptions about study and patient activities and the related expected expenses for those activities determined based on the contracted fees with our service providers. The assumptions we use represent our best estimates of the activity and expenses at the time of our accrual and involve inherent uncertainties and the application of our judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. Our historical accrual estimates have not been materially different from our actual amounts.

Income Taxes

Ionis and Akcea have filed separate U.S. federal income tax returns since Akcea’s IPO in 2017. Accordingly, we were required to assess Ionis’ stand-alone and Akcea’s valuation allowances separately even though we consolidate Akcea’s financial results in our consolidated financial statements. However, as a result of the Akcea Acquisition, Ionis and Akcea will file a consolidated U.S. federal income tax return beginning in the fourth quarter of 2020, and we therefore assessed our U.S. federal valuation allowance requirements on a consolidated basis as of that period. We continue to assess the state portion of our valuation allowance on a consolidated basis.

We assessed our valuation allowance requirements and recorded a valuation allowance of \$313 million against all of Ionis’ U.S. federal net deferred tax assets in the fourth quarter of 2020, due to uncertainties related to our ability to realize the tax benefits associated with these assets. This determination is based largely on Akcea rejoining the Ionis consolidated U.S. federal tax group in the fourth quarter of 2020. Due to Akcea’s historical and projected financial statement losses, and the expected negative impact this will have on Ionis’ consolidated taxable income, there is uncertainty of generating sufficient consolidated pre-tax income in future periods to realize the Ionis deferred tax benefits. It is also expected that Ionis’ pre-tax income in future periods may be lower due to significant investments in research and development associated with our pipeline of wholly owned medicines. We now maintain a valuation allowance against all our consolidated U.S. federal and state net deferred tax assets.

We evaluate our deferred tax assets quarterly to determine whether adjustments to the valuation allowance are appropriate due to changes in facts or circumstances, such as changes in expected future pre-tax earnings, tax law, interactions with taxing authorities and developments in case law. In making this evaluation, we rely on our recent history of pre-tax earnings. Our material assumptions are our forecasts of future pre-tax earnings and the nature and timing of future deductions and income represented by the deferred tax assets and liabilities, all of which involve the exercise of significant judgment. Although we believe our estimates are reasonable, we are required to use significant judgment in determining the appropriate amount of valuation allowance recorded against our deferred tax assets.

Results of Operations

Below we have included our results of operations for 2020 compared to 2019. Refer to our 2019 Form 10-K for our results of operations for 2019 compared to 2018.

Years Ended December 31, 2020 and December 31, 2019

Revenue

Total revenue for 2020 was \$729.3 million compared to \$1.1 billion in 2019 and was comprised of the following (amounts in millions):

	Year Ended December 31,	
	2020	2019
Revenue:		
Commercial revenue:		
SPINRAZA royalties	\$286.6	\$ 293.0
Product sales, net.	70.0	42.3
Licensing and other royalty revenue	<u>8.1</u>	<u>17.2</u>
Total commercial revenue	364.7	352.5
R&D revenue:		
Amortization from upfront payments	79.6	146.2
Milestone payments	182.6	114.9
License fees	86.0	489.7
Other services	<u>16.4</u>	<u>19.3</u>
Total R&D revenue	<u>364.6</u>	<u>770.1</u>
Total revenue	<u>\$729.3</u>	<u>\$1,122.6</u>

In 2020, our commercial revenue increased compared to 2019 primarily due to increases in TEGSEDI and WAYLIVRA product sales, primarily from major market launches in 2020.

We earn our R&D revenue from multiple sources. Our R&D revenue can fluctuate depending on the timing of events. Our R&D revenue in 2020 included more than \$165 million from our cardiometabolic disease franchise, including a \$75 million milestone payment we earned from Pfizer in the fourth quarter of 2020. We also earned more than \$125 million from our neurological disease franchise, primarily driven by several Biogen-partnered programs. Additionally, in November 2020, we completed an arbitration process with Alnylam. The arbitration panel awarded us \$41 million for payments owed to us by Alnylam related to Alnylam's agreement with Sanofi Genzyme. We recognized the \$41 million payment from Alnylam as R&D revenue in the fourth quarter of 2020.

Our R&D revenue in 2019 included significant revenue from license fees, including \$246 million for Pfizer's license of vupanorsen and \$150 million for Novartis' license of pelacarsen. Additionally, our amortization from upfront payments for 2019 was higher compared to 2020 because it included amortization from collaborations for which we have completed our R&D services performance obligations in 2019.

Operating Expenses

Operating expenses for 2020 were \$901.3 million, and increased compared to \$756.7 million for 2019. The increase was principally due to \$89.6 million of operating expenses related to the Akcea Acquisition and restructured European operations, including non-cash stock-based compensation expense of \$59.3 million related to the acceleration of all of Akcea's equity award stock-based compensation expense and severance, retention and other expenses of \$30.3 million. Excluding expenses related to the Akcea Acquisition and restructured European operations, our operating expenses increased primarily due to our investments in the Phase 3 program for IONIS-TTR-L_{Rx} and our wholly-owned pipeline.

Our operating expenses by segment were as follows (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
Ionis Core	\$412.2	\$ 374.0
Akcea Therapeutics	310.9	450.7
Elimination of intercompany activity	<u>(51.9)</u>	<u>(214.6)</u>
Subtotal	671.2	610.1
Non-cash compensation expense related to equity awards	<u>230.1</u>	<u>146.6</u>
Total operating expenses	<u>\$901.3</u>	<u>\$ 756.7</u>

In order to analyze and compare our results of operations to other similar companies, we believe it is important to exclude non-cash compensation expense related to equity awards from our operating expenses. We believe non-cash compensation expense related to equity awards is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Cost of Products Sold

Our cost of products sold consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TEGSEDI and WAYLIVRA and certain associated period costs. Prior to the regulatory approval of TEGSEDI and WAYLIVRA, we expensed as R&D expense a significant portion of the cost of producing TEGSEDI and WAYLIVRA that we are using in the commercial launches. We expect cost of products sold to increase as we deplete these inventories.

Our cost of products sold by segment were as follows (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
Ionis Core	\$ —	\$ —
Akcea Therapeutics	18.9	12.8
Elimination of intercompany activity	<u>(8.9)</u>	<u>(8.9)</u>
Subtotal	10.0	3.9
Non-cash compensation expense related to equity awards	<u>1.9</u>	<u>0.4</u>
Total cost of products sold	<u>\$11.9</u>	<u>\$ 4.3</u>

Our cost of products sold increased in 2020 compared to 2019 because of the increase in associated product sales in the same periods. In its cost of products sold, Akcea includes the amortization for milestone payments it made to us related to the U.S. and European approvals of TEGSEDI. We eliminate this amortization in our consolidated results. All amounts exclude non-cash compensation expense related to equity awards.

We began recognizing cost of products sold for TEGSEDI in the third quarter of 2018 when TEGSEDI was approved and for WAYLIVRA in the second quarter of 2019 when WAYLIVRA was approved. Our cost of products sold increased in 2020 compared to 2019 primarily due to the increase in product sales of TEGSEDI and WAYLIVRA. All amounts exclude non-cash compensation expense related to equity awards.

Research, Development and Patent Expenses

Our research, development and patent expenses consist of expenses for antisense drug discovery, antisense drug development, manufacturing and development chemistry and R&D support expenses.

The following table sets forth information on research, development and patent expenses (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	\$419.5	\$370.3
Non-cash compensation expense related to equity awards	<u>115.6</u>	<u>95.4</u>
Total research, development and patent expenses	<u>\$535.1</u>	<u>\$465.7</u>

Our research, development and patent expenses by segment were as follows (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
Ionis Core	\$325.4	\$ 295.0
Akcea Therapeutics	137.1	281.0
Elimination of intercompany activity	(43.0)	(205.7)
Subtotal	419.5	370.3
Non-cash compensation expense related to equity awards	115.6	95.4
Total research, development and patent expenses	<u>\$535.1</u>	<u>\$ 465.7</u>

Antisense Drug Discovery

We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own antisense drug discovery research, and that of our partners. Antisense drug discovery is also the function that is responsible for advancing our antisense core technology. This function is also responsible for making investments in complementary technologies to expand the reach of antisense technology.

As we continue to advance our antisense technology, we are investing in our drug discovery programs to expand our pipeline.

Our antisense drug discovery expenses are part of our Ionis Core business segment and were as follows (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	\$ 89.2	\$ 83.5
Non-cash compensation expense related to equity awards	24.2	20.9
Total antisense drug discovery expenses	<u>\$113.4</u>	<u>\$104.4</u>

Antisense drug discovery expenses were slightly higher in 2020 compared to 2019 due to expenses we incurred related to advancing our research programs and investments we made in complementary technologies to expand the reach of our antisense technology. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth drug development expenses, including expenses for our marketed medicines and those in Phase 3 development for which we have incurred significant costs (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
TEGSEDI	\$ 14.7	\$ 16.8
WAYLIVRA	5.6	7.4
IONIS-TTR-L _{Rx}	\$ 34.0	\$ 14.1
IONIS-APOCIII-L _{Rx}	5.6	7.6
Other antisense development projects	86.9	86.6
Development overhead expenses	85.9	74.0
Total antisense drug development, excluding non-cash compensation expense related to equity awards	232.7	206.5
Non-cash compensation expense related to equity awards	63.7	45.9
Total antisense drug development expenses	<u>\$296.4</u>	<u>\$252.4</u>

Our development expenses increased in 2020 compared to 2019 primarily due to our broad Phase 3 program for IONIS-TTR-L_{Rx}, which we initiated in late 2019 and other medicines in our wholly-owned pipeline. These increases

were slightly offset by decreases in expenses for TEGSEDI, WAYLIVRA, IONIS-FXI-L_{Rx}, IONIS-APOCIII-L_{Rx} and vupanorsen. We completed a Phase 2 study for IONIS-FXI-L_{Rx} in 2019 and we completed Phase 2 studies for IONIS-APOCIII-L_{Rx} and vupanorsen in early 2020. All amounts exclude non-cash compensation expense related to equity awards.

Our antisense drug development expenses by segment were as follows (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
Ionis Core	\$174.5	\$ 145.0
Akcea Therapeutics	95.7	261.5
Elimination of intercompany activity	<u>(37.5)</u>	<u>(200.0)</u>
Subtotal	232.7	206.5
Non-cash compensation expense related to equity awards	<u>63.7</u>	<u>45.9</u>
Total antisense drug development expenses	<u>\$296.4</u>	<u>\$ 252.4</u>

We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials, we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are clinical research programs that fuel our Phase 3 pipeline. When our medicines are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state in which we may adjust the development strategy for each medicine. Although we may characterize a medicine as “in Phase 1” or “in Phase 2,” it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous medicines based on each medicine’s particular needs at that time. This means we are constantly shifting resources among medicines. Therefore, what we spend on each medicine during a particular period is usually a function of what is required to keep the medicines progressing in clinical development, not what medicines we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one medicine to another and cannot be used to accurately predict future costs for each medicine. And, because we always have numerous medicines in preclinical and early stage clinical research, the fluctuations in expenses from medicine to medicine, in large part, offset one another. If we partner a medicine, it may affect the size of a trial, its timing, its total cost and the timing of the related costs.

Manufacturing and Development Chemistry

Expenditures in our manufacturing and development chemistry function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. Our manufacturing and development chemistry function is responsible for providing drug supplies to antisense drug development and our collaboration partners. Our manufacturing procedures include testing to satisfy good laboratory and good manufacturing practice requirements.

Our manufacturing and development chemistry expenses were as follows (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	\$55.9	\$42.5
Non-cash compensation expense related to equity awards	<u>10.9</u>	<u>9.6</u>
Total manufacturing and development chemistry expenses	<u>\$66.8</u>	<u>\$52.1</u>

Manufacturing and development chemistry expenses increased in 2020 compared to 2019. The increase in manufacturing and development chemistry expenses was primarily related to manufacturing API for IONIS-TTR-L_{Rx} and IONIS-APOCIII-L_{Rx} for our Phase 3 studies. All amounts exclude non-cash compensation expense related to equity awards.

Our manufacturing and development chemistry expenses by segment were as follows (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
Ionis Core	\$42.6	\$36.8
Akcea Therapeutics	18.6	11.2
Elimination of intercompany activity	<u>(5.3)</u>	<u>(5.5)</u>
Subtotal	55.9	42.5
Non-cash compensation expense related to equity awards	<u>10.9</u>	<u>9.6</u>
Total manufacturing and development chemistry expenses	<u>\$66.8</u>	<u>\$52.1</u>

R&D Support

In our research, development and patent expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, informatics costs, procurement costs and waste disposal costs. We call these costs R&D support expenses.

The following table sets forth information on R&D support expenses (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
Personnel costs	\$14.7	\$15.2
Occupancy	10.2	9.4
Patent expenses	4.1	4.2
Insurance	2.4	1.8
Computer software and licenses	2.9	1.1
Other	<u>7.4</u>	<u>6.1</u>
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	41.7	37.8
Non-cash compensation expense related to equity awards	<u>16.8</u>	<u>19.0</u>
Total R&D support expenses	<u>\$58.5</u>	<u>\$56.8</u>

R&D support expenses for 2020 increased compared to 2019 primarily due to costs from growth in our operations. All amounts exclude non-cash compensation expense related to equity awards.

Our R&D support expenses by segment were as follows (in millions):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
Ionis Core	\$19.2	\$29.7
Akcea Therapeutics	22.7	8.3
Elimination of intercompany activity	<u>(0.2)</u>	<u>(0.2)</u>
Subtotal	41.7	37.8
Non-cash compensation expense related to equity awards	<u>16.8</u>	<u>19.0</u>
Total R&D support expenses	<u>\$58.5</u>	<u>\$56.8</u>

Selling, General and Administrative Expenses

Selling, general and administrative, or SG&A, expenses include personnel and outside costs associated with the pre-commercialization and commercialization activities for our medicines and costs to support our company, our employees and our stockholders including, legal, human resources, investor relations, and finance. Additionally, we include in selling, general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation and utilities costs that we need to support the corporate functions listed above. We also include fees we owe under our in-licensing agreements related to SPINRAZA.

The following table sets forth information on SG&A expenses (in millions):

	Year Ended December 31,	
	2020	2019
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	\$241.8	\$235.8
Non-cash compensation expense related to equity awards	<u>112.5</u>	<u>50.8</u>
Total selling, general and administrative expenses	<u>\$354.3</u>	<u>\$286.6</u>

SG&A expenses were slightly higher for 2020 compared to 2019 principally due to costs related to the Akcea Acquisition, including severance and retention costs and legal costs related to the Alnylam arbitration. These increases were mostly offset by reductions in travel and marketing events as a result of the COVID-19 pandemic. All amounts exclude non-cash compensation expense related to equity awards.

Our SG&A expenses by segment were as follows (in millions):

	Year Ended December 31,	
	2020	2019
Ionis Core	\$ 86.8	\$ 78.9
Akcea Therapeutics	<u>155.0</u>	<u>156.9</u>
Subtotal	241.8	235.8
Non-cash compensation expense related to equity awards	<u>112.5</u>	<u>50.8</u>
Total selling general and administrative expenses	<u>\$354.3</u>	<u>\$286.6</u>

Akcea Therapeutics, Inc.

The following table sets forth information on operating expenses (in millions) for our Akcea Therapeutics business segment:

	Year Ended December 31,	
	2020	2019
Cost of products sold	\$ 18.9	\$ 12.8
Development and patent expenses	99.6	81.0
Sublicense fees to Ionis	37.5	200.0
Selling, general and administrative expenses	155.0	156.9
Profit (loss) share for TEGSEDI commercialization activities	<u>(16.2)</u>	<u>(37.3)</u>
Total operating expenses, excluding non-cash compensation expense related to equity awards	294.8	413.4
Non-cash compensation expense related to equity awards	<u>94.8</u>	<u>37.1</u>
Total Akcea Therapeutics operating expenses	<u>\$389.6</u>	<u>\$450.5</u>

See discussion of fluctuations of Akcea operating expenses in the operating expense sections above. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for 2020 was \$30.6 million compared to \$52.0 million for 2019. The decrease in investment income was primarily due to a decrease in interest rates during 2020 compared to 2019.

Interest Expense

The following table sets forth information on interest expense (in millions):

	Year Ended December 31,	
	2020	2019
Convertible senior notes:		
Non-cash amortization of the debt discounts and debt issuance costs	\$38.7	\$39.3
Interest expense payable in cash.	3.8	6.7
Interest on mortgage for primary R&D and manufacturing facilities.	2.4	2.4
Other	<u>0.1</u>	<u>0.4</u>
Total interest expense	<u>\$45.0</u>	<u>\$48.8</u>

Our interest expense payable in cash decreased in 2020 compared 2019 because we exchanged a significant portion of our 1% Notes for 0.125% Notes in December 2019.

Gain on Investments

Gain on investments for 2020 was \$16.5 million compared to \$0.2 million for 2019. During the second and fourth quarters of 2020, we revalued our investments in three privately held companies, Dynacure, Suzhou-Ribo and Aro Biotherapeutics because the companies sold additional equity securities that were similar to the equity we own. Because of these observable price changes we recognized a \$6.3 million gain on our investment in Dynacure, a \$3.0 million gain on our investment in Suzhou-Ribo and a \$5.5 million gain on our investment in Aro Biotherapeutics in our consolidated statement of operations during 2020 because the sales were at higher prices compared to our recorded value.

Early Retirement of Debt

As a result of the debt exchange we completed in December 2019, we recorded a \$21.9 million non-cash loss on early retirement of debt, reflecting the early retirement of a portion of our 1% Notes. The non-cash loss on the early retirement of our debt is the difference between the amount paid to exchange our 1% Notes that we attributed to the liability component and the net carrying balance of the liability component at the time that we completed the debt exchange.

Income Tax Expense (Benefit)

We had income tax expense of \$316.7 million for 2020 compared to an income tax expense of \$43.5 million for 2019. Our 2020 income tax expense primarily relates to a non-cash tax expense of \$313 million related to an increase in the valuation allowance recorded against Ionis' U.S. federal net deferred tax assets in the fourth quarter of 2020. We now maintain a valuation allowance against all our consolidated U.S. federal and state net deferred tax assets. See discussion of our valuation allowance under the section titled, *Income Taxes*, above in our discussion of our critical accounting estimates.

Net Income (Loss)

We generated a net loss of \$486.8 million for 2020 compared to net income of \$303.3 million for 2019. Our net loss for 2020 was primarily due to the valuation allowance we recorded as a result of the Akcea Acquisition, as discussed above in the income tax expense section. Also contributing to our net loss in 2020 was decreased revenue year-over-year, as discussed above in the revenue section and an increase in operating expenses year-over-year, as discussed above in the operating expense section.

Net Income (Loss) Attributable to Noncontrolling Interest in Akcea Therapeutics, Inc.

Our noncontrolling interest in Akcea on our statement of operations for 2020 was a net loss of \$35.5 million compared to net income of \$9.1 million for 2019. The net loss attributable to noncontrolling interest in Akcea for the year ended December 31, 2020, represents the portion of Akcea's net loss that third parties owned for the period from January 1, 2020 until we acquired 100 percent of Akcea in October 2020. After our acquisition of Akcea in October 2020, we no longer recorded any adjustment related to noncontrolling interest for Akcea's net loss. Akcea generated net income in 2019 primarily because it earned significant license fee revenue from Novartis and Pfizer.

Net Income (Loss) Attributable to Ionis Pharmaceuticals, Inc. Common Stockholders and Net Income (Loss) per Share

We had a net loss attributable to our common stockholders of \$451.3 million for 2020 compared to net income of \$294.1 million in 2019. Basic and diluted net loss per share for 2020 were each \$3.23. Basic and diluted net income per share for 2019 was \$2.12 and \$2.08, respectively.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also finance our operations from commercial revenue from SPINRAZA royalties and product sales. From our inception through December 31, 2020, we have earned approximately \$5.0 billion in revenue. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through December 31, 2020, we have raised net proceeds of approximately \$2.0 billion from the sale of our equity securities. Additionally, we borrowed approximately \$1.5 billion under long-term debt arrangements to finance a portion of our operations over the same time period.

Our key liquidity metrics and capital resources include our cash, cash equivalents and short-term investments, working capital and debt obligations. During 2020 we used a portion of our cash to complete the Akcea Acquisition. At December 31, 2020, we had \$1.9 billion of cash and short-term investments on hand. We believe our cash and short-term investment balance is sufficient to fund our operations both in the short-term (i.e., the next 12 months) and in the long-term (i.e., beyond the next 12 months). In 2020 our working capital decreased because our cash and investments decreased and our 1% Notes became a current liability.

The following table summarizes our contractual obligations as of December 31, 2020. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

Contractual Obligations (selected balances described below)	Payments Due by Period (in millions)		
	Total	Less than 1 year	More than 1 year
1% Notes (principal and interest payable)	\$313.0	\$313.0	\$ —
0.125% Notes (principal and interest payable)	551.6	0.7	550.9
Building mortgage payments	75.8	2.4	73.4
Other obligations (principal and interest payable).	0.9	0.1	0.8
Operating leases.	<u>23.3</u>	<u>3.3</u>	<u>20.0</u>
Total	<u>\$964.6</u>	<u>\$319.5</u>	<u>\$645.1</u>

Our contractual obligations consist primarily of our convertible debt. In addition, we also have facility mortgages, facility leases, equipment financing arrangements and other obligations. Due to the uncertainty with respect to the timing of future cash outflows associated with our unrecognized tax benefits, we are unable to make reasonably reliable estimates of the period of cash settlement with the respective taxing authorities. Therefore, we have excluded our gross unrecognized tax benefits from our contractual obligations table above. We have not entered into, nor do we currently have, any off-balance sheet arrangements (as defined under SEC rules).

0.125 Percent Convertible Senior Notes and Call Spread

In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange \$375.6 million of our 1% Notes for \$439.3 million of our 0.125% Notes, and to issue \$109.5 million of our 0.125% Notes. We completed this exchange to reduce our cash interest payments, increase our conversion price and extend our maturity for a large portion of our debt. Additionally, in conjunction with the December 2019 exchange, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the conversion price on our 0.125% Notes even further. We accounted for our call spread transactions using the Derivatives and Hedging – Contracts in Entity’s Own Equity accounting guidance contained in Topic 815. We determined that the call spread transactions meet the definition of a derivative, are indexed to our stock and meet the criteria to be classified in shareholders’ equity.

The call spread cost us \$52.6 million of which \$108.7 million was for the note hedge purchase offset by \$56.1 million we received for selling the warrants. We increased our effective conversion price to \$123.38 with the same number of underlying shares as our 0.125% Notes.

Similar to our 0.125% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0.125% Notes. The note hedges will expire upon maturity of the 0.125% Notes, or December 2024. The note hedges and warrants are separate transactions and are not part of the terms of our 0.125% Notes. The holders of the 0.125% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the aggregate amount paid for the note hedges and the aggregate amount received for the warrants in additional paid-in capital in our consolidated balance sheet. See our Call Spread accounting policy in Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period. We excluded shares under the note hedges from our calculation of diluted earnings per share as they were antidilutive. We will include the shares issuable under the warrants in our calculation of diluted earnings per share when the average market price per share of our common stock for the reporting period exceeds the strike price of the warrants.

At December 31, 2020, we had the following 0.125% Notes outstanding (amounts in millions except price per share data):

	<u>0.125% Notes</u>
Outstanding principal balance	\$548.8
Maturity date	December 2024
Interest rate	0.125 percent
Conversion price per share	\$83.28
Total shares of common stock subject to conversion	6.6

Interest is payable semi-annually for the 0.125% Notes. The 0.125% Notes are convertible under certain conditions, at the option of the note holders. We can settle conversions of the 0.125% Notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the 0.125% Notes prior to maturity, and no sinking fund is provided for them. Holders of the 0.125% Notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 0.125% Notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

1 Percent Convertible Senior Notes

In November 2014, we completed a \$500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. In December 2016, we issued an additional \$185.5 million of 1% Notes in exchange for the redemption of a portion of our previously outstanding 2¾% Notes. In December 2019, we exchanged a portion of our 1% Notes for new 0.125% Notes.

At December 31, 2020, we had the following 1% Notes outstanding (amounts in millions except price per share data):

	<u>1% Notes</u>
Outstanding principal balance	\$309.9
Maturity date	November 2021
Interest rate	1 percent
Conversion price per share	\$66.81
Total shares of common stock subject to conversion	4.6

Interest is payable semi-annually for the 1% Notes. The 1% Notes are convertible under certain conditions, at the option of the note holders. We settle conversions of the 1% Notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the 1% Notes prior to maturity, and no sinking fund is provided for them. Holders of the 1% Notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indenture governing the 1% Notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

Research and Development and Manufacturing Facilities

In July 2017, we purchased the building that houses our primary R&D facility for \$79.4 million and our manufacturing facility for \$14.0 million. We financed the purchase of these two facilities with mortgage debt of \$60.4 million in total. Our primary R&D facility mortgage has an interest rate of 3.88 percent. Our manufacturing facility mortgage has an interest rate of 4.20 percent. During the first five years of both mortgages, we are only required to make interest payments. Both mortgages mature in August 2027.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2020 for the purchase of services, capital equipment and materials as part of our normal course of business.

We may enter into additional collaborations with partners which could provide for additional revenue to us and we may incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash, cash equivalents and short-term investments to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to changes in interest rates primarily from our investments in certain short-term investments. We primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury and reputable financial institutions, corporations, and U.S. government agencies with strong credit ratings. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

Item 8. Financial Statements and Supplementary Data

We filed our consolidated financial statements and supplementary data required by this item as exhibits hereto, and listed them under Item 15(a)(1) and (2), and incorporate them herein by reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

We maintain disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or Exchange Act) that are designed to ensure that information we are required to disclose in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. We designed and evaluate our disclosure controls and procedures recognizing that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance and not absolute assurance of achieving the desired control objectives.

As of the end of the period covered by this report on Form 10-K, we carried out an evaluation of our disclosure controls and procedures under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of December 31, 2020.

Management’s Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Exchange Act Rules 13a-15(f). Our internal control over financial reporting is a process designed under the supervision of our Chief Executive Officer and Chief Financial Officer to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external purposes in accordance with U.S. generally accepted accounting principles.

As of December 31, 2020, we assessed the effectiveness of our internal control over financial reporting based on the criteria for effective internal control over financial reporting under the 2013 “Internal Control—Integrated Framework,” issued by the Committee of Sponsoring Organizations, or COSO, of the Treadway Commission, under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on that assessment, our management concluded that we maintained effective internal control over financial reporting as of December 31, 2020.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2020, as stated in their attestation report, which is included elsewhere herein.

Changes in Internal Control over Financial Reporting

The above assessment did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

Opinion on Internal Control over Financial Reporting

We have audited Ionis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2020, based on criteria established in Internal Control — Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Ionis Pharmaceuticals, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2020, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2020 and 2019, and the related consolidated statements of operations, comprehensive income (loss), stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2020, and the related notes and our report dated February 24, 2021 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the 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 audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

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 (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) 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 (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

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

/s/ Ernst & Young LLP

San Diego, California
February 24, 2021

Item 9B. Other Information

Not applicable.

PART III**Item 10. Directors, Executive Officers and Corporate Governance**

We incorporate by reference the information required by this Item with respect to directors and the Audit Committee from the information under the caption “ELECTION OF DIRECTORS,” including in particular the information under “Nominating, Governance and Review Committee” and “Audit Committee,” contained in our definitive Proxy Statement, which we will file with the Securities and Exchange Commission within 120 days after the end of the fiscal year ended December 31, 2020, or the Proxy Statement.

We incorporate by reference the required information concerning our Code of Ethics from the information under the caption “Code of Ethics and Business Conduct” contained in the Proxy Statement. Our Code of Ethics and Business Conduct is posted on our website at www.ionispharma.com⁽¹⁾. We intend to disclose future amendments to, or waivers from, our Code of Ethics and Business Conduct on our website.

Delinquent Section 16(a) Reports

Item 1, Part I of this Report contains information concerning our executive officers. We incorporate by reference the information required by this Item concerning compliance with Section 16(a) of the Exchange Act from the information under the caption “Delinquent Section 16(a) Reports” contained in the Proxy Statement.

Item 11. Executive Compensation

We incorporate by reference the information required by this item to the information under the caption “EXECUTIVE COMPENSATION,” “Compensation Committee Interlocks and Insider Participation” and “COMPENSATION COMMITTEE REPORT” contained in the Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

We incorporate by reference the information required by this item to the information under the captions “SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT” contained in the Proxy Statement.

Securities Authorized for Issuance under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2020.

<u>Plan Category</u>	<u>Number of Shares to be Issued Upon Exercise of Outstanding Options</u>	<u>Weighted Average Exercise Price of Outstanding Options</u>	<u>Number of Shares Remaining Available for Future Issuance</u>
Equity compensation plans approved by stockholders ^(a)	<u>12,394,777</u>	\$54.11	<u>8,325,343</u> ^(b)
Total	<u>12,394,777</u>	\$54.11	<u>8,325,343</u>

(a) Consists of five Ionis plans: 1989 Stock Option Plan, Amended and Restated 2002 Non-Employee Directors’ Stock Option Plan, 2011 Equity Incentive Plan, 2020 Equity Incentive Plan and Employee Stock Purchase Plan, or ESPP.

(b) Of these shares, 662,511 remained available for purchase under the ESPP as of December 31, 2020.

⁽¹⁾ Any information that is included on or linked to our website is not part of this Form 10-K.

For additional details about our equity compensation plans, including a description of each plan, see Note 4, *Stockholders' Equity*, in the Notes to the Consolidated Financial Statements.

Item 13. Certain Relationships and Related Transactions, and Director Independence

We incorporate by reference the information required by this item to the information under the captions “Independence of the Board of Directors” and “Certain Relationships and Related Transactions” contained in the Proxy Statement.

Item 14. Principal Accounting Fees and Services

We incorporate by reference the information required by this item to the information under the caption “Ratification of Selection of Independent Auditors” contained in the Proxy Statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Index to Financial Statements

We submitted the consolidated financial statements required by this item in a separate section beginning on page F-1 of this Report.

(a)(2) Index to Financial Statement Schedules

We omitted these schedules because they are not required, or are not applicable, or the required information is shown in the consolidated financial statements or notes thereto.

(a)(3) Index to Exhibits

INDEX TO EXHIBITS

<u>Exhibit Number</u>	<u>Description of Document</u>
2.1	Agreement and Plan of Merger, dated as of August 30, 2020, among Akcea Therapeutics, Inc., Ionis Pharmaceuticals, Inc. and Avalanche Merger Sub, Inc., filed as an exhibit to the Registrant's Current Report on Form 8-K filed August 31, 2020 and incorporated herein by reference.
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
3.2	Certificate of Amendment to Restated Certificate of Incorporation, filed June 17, 2014. - Filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement, for the 2014 Annual Meeting of Stockholders, filed with the SEC on April 25, 2014 and incorporated herein by reference.
3.3	Certificate of Amendment to Restated Certificate of Incorporation, filed December 18, 2015. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 18, 2015 and incorporated herein by reference.
3.4	Amended and Restated Bylaws, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 18, 2015 and incorporated herein by reference.
4.1	Certificate of Designation of the Series C Junior Participating Preferred Stock, filed as an exhibit to Registrant's Report on Form 8-K filed December 13, 2000 and incorporated herein by reference.
4.2	Specimen Common Stock Certificate, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
4.3	Indenture, dated as of November 17, 2014, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 1.00 percent Convertible Senior Note due 2021, filed as an exhibit to the Registrant's Current Report on Form 8-K filed November 21, 2014 and incorporated herein by reference.
4.4	Indenture, dated as of December 19, 2019, by and between Ionis Pharmaceuticals, Inc. and U.S. Bank National Association, as trustee, including Form of 0.125 percent Convertible Senior Note due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 23, 2019 and incorporated herein by reference.
4.5	Form of Exchange and/or Subscription Agreement for Ionis Pharmaceuticals, Inc. Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.

Exhibit Number	Description of Document
4.6	Form of Convertible Note Hedge Transactions Confirmation, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.7	Form of Warrant Transactions Confirmation, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.8	Description of the Registrant's Securities, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2019 and incorporated herein by reference.
10.1	Form of Indemnity Agreement entered into between the Registrant and its Directors and Officers with related schedule, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference.
10.2*	Registrant's 1989 Stock Option Plan, as amended, filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2012 Annual Meeting of Stockholders, filed with the SEC on April 16, 2012 and incorporated herein by reference.
10.3*	Registrant's Amended and Restated 2000 Employee Stock Purchase Plan, filed as an exhibit to Registrant's Current Report on Form 8-K filed with the SEC on March 26, 2019 and incorporated herein by reference.
10.4	Form of Employee Confidential Information and Inventions Agreement, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
10.5	Amendment #1 to the Research, Development and License Agreement dated May 11, 2011 by and between the Registrant and Glaxo Group Limited, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2011 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.6	Amended and Restated Collaboration and License Agreement between the Registrant and Antisense Therapeutics Ltd dated February 8, 2008, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2008 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.7	Strategic Collaboration, Option and License Agreement by and among Akcea Therapeutics, Inc. and Novartis Pharma AG, dated January 5, 2017, filed as an exhibit to Akcea Therapeutics, Inc.'s Form S-1 filed March 27, 2017 and incorporated herein by reference.
10.8	Amendment No. 1 to the Strategic Collaboration, Option and License Agreement between Akcea Therapeutics, Inc. and Novartis Pharma AG dated February 22, 2019, filed as an exhibit to Akcea Therapeutics, Inc.'s Quarterly Report on Form 10-Q for the quarter ended March 30, 2019 and incorporated herein by reference.
10.9	Stock Purchase Agreement among the Registrant, Akcea Therapeutics, Inc. and Novartis Pharma AG dated January 5, 2017, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 and incorporated herein by reference.
10.10	Amendment #1 between the Registrant and Bayer AG dated February 10, 2017, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

Exhibit Number	Description of Document
10.11	Registrant's Amended and Restated 10b5-1 Trading Plan dated September 12, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013 and incorporated herein by reference.
10.12*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended, filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement for the 2020 Annual Meeting of Stockholders, filed with the SEC on April 24, 2020 and incorporated herein by reference.
10.13*	Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, filed as an exhibit to the Registrant's Form S-8 filed on August 7, 2020 and incorporated herein by reference.
10.14	Research Collaboration, Option and License Agreement between the Registrant and Biogen MA Inc. dated December 19, 2017, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.15*	Amended and Restated Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Notice of 2019 Annual Meeting of Stockholders and Proxy Statement filed with the SEC on April 26, 2019 and incorporated herein by reference.
10.16*	Form of Option Agreement under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference.
10.17*	Form of Time-Vested Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed with the SEC on August 8, 2011 and incorporated herein by reference.
10.18*	Forms of Performance Based Restricted Stock Unit Grant Notice and Performance Based Restricted Stock Unit Agreement for Performance Based Restricted Stock Units granted under the 2011 Equity Incentive Plan.
10.19*	Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.20*	Form of Global Option Agreement for options granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.21*	Form of Global Restricted Stock Unit Agreement for restricted stock units granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.22*	Forms of Restricted Stock Unit Grant Notice, Stock Option Grant Notice and Stock Option Exercise Notice for options granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.23	Loan Agreement between Ionis Gazelle, LLC and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.24*	Form of Option Agreement under the 1989 Stock Option Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference.

Exhibit Number	Description of Document
10.25*	Form of Option Agreement for Options granted under the 2002 Non-Employee Director's Stock Option Plan, filed as an exhibit to the Registrant's Form S-8 filed on August 7, 2020 and incorporated herein by reference.
10.26	Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated March 30, 2010, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2010 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.27	Loan Agreement between Ionis Faraday, LLC and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.28	Research Agreement dated August 10, 2011 between the Registrant and CHDI Foundation, Inc, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2011 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.29	Guaranty between the Registrant and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.30	Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated January 3, 2012, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.31	DMPK Research, Development, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated June 27, 2012, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.32	Amendment #2 to Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated October 30, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.33	Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated December 7, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.34	Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated December 10, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.35	HTT Research, Development, Option and License Agreement among the Registrant, F. Hoffmann-La Roche Ltd and Hoffman-La Roche Inc. dated April 8, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

Exhibit Number	Description of Document
10.36	Letter Agreement between the Registrant and CHDI Foundation, Inc. dated April 8, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.37	Amendment #1 to Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated August 13, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.38	Letter Agreement Amendment between the Registrant and Biogen Idec International Holding Ltd dated January 27, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.39	Amendment No. 3 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated July 10, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.40	Amendment #4 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated April 10, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.41	Amendment #5 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated June 27, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.42	Exclusive License Agreement between the Registrant and the University of Massachusetts dated January 14, 2010, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.43	Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated October 26, 2011, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.44	Amendment to Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated March 14, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.45	Amendment #1 to the Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated December 15, 2014, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

Exhibit Number	Description of Document
10.46	Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 22, 2014. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.47	Amendment No.2 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated October 15, 2014, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.48	Strategic Collaboration Agreement between the Registrant and AstraZeneca AB dated July 31, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.49	Amendment #6 to Research, Development and License Agreement between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated September 2, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.50	Amendment Number One to the Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated July 13, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.51	License Agreement between the Registrant and Bayer Pharma AG dated May 1, 2015. Portions of this exhibit have been omitted and separately filed with the SEC, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.52	Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated January 8, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.53	Amendment #1 to HTT Research, Development, Option and License Agreement between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. dated January 9, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.54	Amendment No.3 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated January 18, 2016, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.55	Amendment #7 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated March 4, 2016, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

Exhibit Number	Description of Document
10.56	First Amendment to Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 21, 2016. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.57	Letter Agreement between the Registrant and Biogen MA Inc. dated October 28, 2016, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.58	Guaranty between the Registrant and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.59	Environmental Indemnity Agreement among the Registrant, Ionis Gazelle, LLC and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.60*	Registrant's Severance Benefit Plan and Summary Plan Description dated October 18, 2018, filed as an exhibit to the Registrant's Current Report on form 8-K filed October 18, 2018 and incorporated herein by reference.
10.61	Third Amended and Restated Strategic Advisory Services Agreement by and between the Registrant and B. Lynne Parshall, dated February 22, 2021
10.62	Development, Commercialization, Collaboration, and License Agreement by and between the Registrant and Akcea Therapeutics, Inc., dated March 14, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 and incorporated herein by reference.
10.63	Amended and Restated Services Agreement by and between the Registrant and Akcea Therapeutics, Inc., dated March 14, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 and incorporated herein by reference.
10.64	New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated April 19, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.65	Stock Purchase Agreement by and between the Registrant and Biogen MA Inc., dated April 19, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2018 and incorporated herein by reference.
10.66	Second Amendment to Research, Collaboration, Option and License Agreement by and between the Registrant and Janssen Biotech Inc., dated August 7, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.67	Factor B Development Collaboration, Option and License Agreement by and between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., dated October 9, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

Exhibit Number	Description of Document
10.68	Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated October 17, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.69	Amendment #1 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.70	Amendment #4 to the Collaboration, License and Development Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.71	Amendment #1 to Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated May 2, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2019 and incorporated herein by reference.
10.72	Amendment #1 to the New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen MA Inc., dated August 16, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.73	Amendment #8 to the Research, Development and License Agreement between the Registrant, Glaxo Group Limited and Glaxosmithkline Intellectual Property Development Limited, dated July 29, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.74	Consent to Collateral Addition and Amendment to Loan Documents between the Registrant, Ionis Gazelle, LLC, Wells Fargo Bank, National Association, as Trustee for the Benefit of the Registered Holders of UBS Commercial Mortgage Trust 2017-C3, Commercial Mortgage Pass-Through Certificates, Series 2017-C3, dated August 1, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference.
10.75	License Agreement by and among Akcea Therapeutics, Inc. and Pfizer Inc. dated October 4, 2019, filed as an exhibit to Akcea Therapeutics, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2019 and incorporated herein by reference.
10.76	Letter Agreement between the Registrant, Akcea Therapeutics, Inc., and Pfizer Inc., dated October 4, 2019, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.77	Side Letter dated June 11, 2020 to the Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated October 17, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.

Exhibit Number	Description of Document
10.78	Amendment No. 2 dated April 30, 2020 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB dated July 31, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.79	Amendment No. 3 dated December 17, 2020 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB dated July 31, 2015. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.80	Strategic Advisory Services Agreement by and between the Registrant and Stanley T. Crooke, dated December 17, 2020.
10.81	Side Letter dated December 31, 2020 to the New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated April 19, 2018. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney – Included on the signature page of this Annual Report on Form 10-K.
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1+	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2020, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of comprehensive income (loss), (iv) consolidated statements of stockholders' equity (v) consolidated statements of cash flows, and (vi) notes to consolidated financial statements (detail tagged)
104	Cover Page Interactive Data File (formatted in iXBRL and included in exhibit 101)

* Indicates management compensatory plans and arrangements as required to be filed as exhibits to this Report pursuant to Item 14(c).

† This certification is deemed not filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended.

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 on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 24th day of February, 2021.

IONIS PHARMACEUTICALS, INC.

By: /s/ BRETT P. MONIA
Brett P. Monia., Ph.D.
Chief Executive Officer (Principal executive officer)

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Brett P. Monia and Elizabeth L. Hougen, or any of them, his or her attorney-in-fact, each with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Report, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

<u>Signatures</u>	<u>Title</u>	<u>Date</u>
<u>/s/ BRETT P. MONIA</u> Brett P. MONIA, Ph.D.	Director and Chief Executive Officer (Principal executive officer)	February 24, 2021
<u>/s/ ELIZABETH L. HOUGEN</u> Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	February 24, 2021
<u>/s/ STANLEY T. CROOKE</u> Stanley T. Crooke, M.D., Ph.D.	Executive Chairman of the Board	February 24, 2021
<u>/s/ B. LYNNE PARSHALL</u> B. Lynne Parshall, J.D.	Director and Senior Strategic Advisor	February 24, 2021
<u>/s/ SPENCER R. BERTHELSEN</u> Spencer R. Berthelsen, M.D.	Director	February 24, 2021
<u>/s/ BREAUX CASTLEMAN</u> Breaux Castleman	Director	February 24, 2021
<u>/s/ MICHAEL HAYDEN</u> Michael Hayden, CM OBC MB ChB PhD FRCP(C) FRSC	Director	February 24, 2021
<u>/s/ JOAN E. HERMAN</u> Joan E. Herman	Director	February 24, 2021

<u>Signatures</u>	<u>Title</u>	<u>Date</u>
<u>/s/ JOSEPH KLEIN</u> Joseph Klein, III	Director	February 24, 2021
<u>/s/ JOSEPH LOSCALZO</u> Joseph Loscalzo, M.D., Ph.D.	Director	February 24, 2021
<u>/s/ FREDERICK T. MUTO</u> Frederick T. Muto, Esq.	Director	February 24, 2021
<u>/s/ PETER N. REIKES</u> Peter N. Reikes	Director	February 24, 2021
<u>/s/ JOSEPH H. WENDER</u> Joseph H. Wender	Director	February 24, 2021

IONIS PHARMACEUTICALS, INC.

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Ionis Pharmaceuticals, Inc. (the “Company”) as of December 31, 2020 and 2019, the related consolidated statements of operations, comprehensive income (loss), stockholders’ equity, and cash flows, for each of the three years in the period ended December 31, 2020 and the related notes (collectively referred to as the “consolidated financial statements”). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2020 and 2019, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2020, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company’s internal control over financial reporting as of December 31, 2020, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), and our report dated February 24, 2021 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company’s management. Our responsibility is to express an opinion on the Company’s financial statements based on our audits. We are a public accounting firm registered with the 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 audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures include examining, on a test basis, evidence regarding the amounts and disclosures in the 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 financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter 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 account or disclosure to which it relates.

Realizability of Deferred Tax Assets

Description of the Matter As discussed in Note 1 to the consolidated financial statements, the Company records a valuation allowance based on the assessment of the realizability of the Company’s deferred tax assets. Deferred tax assets are reduced by a valuation allowance if, based on the weight of all available evidence, in management’s judgment it is more likely than not that some portion, or all, of the deferred tax assets will not be realized. For the year ended December 31, 2020, the Company had net deferred tax assets of \$633.4 million and a related valuation allowance of \$633.4 million as described in Note 5.

Auditing management’s assessment of the realizability of its deferred tax assets involved significant judgment because the assessment process is complex, and is based upon assumptions that may be affected by future market or economic conditions.

How We Addressed the Matter in Our Audit We evaluated and tested the design and operating effectiveness of controls over the Company's income tax process, including controls over management's scheduling of the future reversal of existing taxable temporary differences, identification and use of available tax planning strategies and projections of future taxable income (loss).

Among other audit procedures performed, we evaluated the assumptions used by the Company to develop the scheduling of the future reversal of existing taxable temporary differences, tax planning strategies, as well as current earnings and anticipated future earnings (losses) used in the Company's analysis in determining the valuation allowance on a jurisdiction by jurisdiction basis. We tested the completeness and accuracy of the underlying data used in the Company's projections. For example, we compared management's forecasts to actual results for the current and historical periods. Furthermore, we evaluated the appropriateness of the assumptions underlying the future projected financial information, as well as management's consideration of current operating, industry and economic trends. We also compared the projections of future taxable income (loss) with other forecasted financial information prepared by the Company. In addition, we involved our tax specialists to evaluate the application of tax law in the projections of future taxable income (loss).

/s/ Ernst & Young LLP

We have served as the Company's auditor since 1989

San Diego, California

February 24, 2021

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share data)

	December 31,	
	2020	2019
ASSETS		
Current assets:		
Cash and cash equivalents	\$ 397,664	\$ 683,287
Short-term investments	1,494,711	1,816,257
Contracts receivable	76,204	63,034
Inventories	21,965	18,180
Other current assets	140,163	139,839
Total current assets	2,130,707	2,720,597
Property, plant and equipment, net	181,077	153,651
Patents, net	27,937	25,674
Long-term deferred tax assets	—	305,557
Deposits and other assets	50,034	27,633
Total assets	\$ 2,389,755	\$3,233,112
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	\$ 17,199	\$ 16,067
Accrued compensation	65,728	37,357
Accrued liabilities	90,161	66,769
Income taxes payable	1,324	32,514
1 percent convertible senior notes	293,161	—
Current portion of long-term obligations	7,301	2,026
Current portion of deferred contract revenue	108,376	118,272
Total current liabilities	583,250	273,005
Long-term deferred contract revenue	424,046	490,060
0.125 percent convertible senior notes	455,719	434,711
1 percent convertible senior notes	—	275,333
Long-term obligations, less current portion	23,409	15,543
Long-term mortgage debt	59,984	59,913
Total liabilities	1,546,408	1,548,565
Stockholders' equity:		
Common stock, \$0.001 par value; 300,000,000 shares authorized, 140,365,594 and 140,339,615 shares issued and outstanding at December 31, 2020 and December 31, 2019, respectively	140	140
Additional paid-in capital	2,113,646	2,203,778
Accumulated other comprehensive loss	(21,071)	(25,290)
Accumulated deficit	(1,249,368)	(707,534)
Total Ionis stockholders' equity	843,347	1,471,094
Noncontrolling interest in Akcea Therapeutics, Inc.	—	213,453
Total stockholders' equity	843,347	1,684,547
Total liabilities and stockholders' equity	\$ 2,389,755	\$3,233,112

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(In thousands, except for per share amounts)

	Year Ended December 31,		
	2020	2019	2018
Revenue:			
Commercial revenue:			
SPINRAZA royalties	\$ 286,583	\$ 292,992	\$237,930
Product sales, net.	69,999	42,253	2,237
Licensing and other royalty revenue	8,117	17,205	14,755
Total commercial revenue	364,699	352,450	254,922
Research and development revenue under collaborative agreements	364,565	770,149	344,752
Total revenue	729,264	1,122,599	599,674
Expenses:			
Cost of products sold	11,947	4,384	1,820
Research, development and patent	535,077	465,688	414,604
Selling, general and administrative.	354,322	286,644	244,622
Total operating expenses	901,346	756,716	661,046
Income (loss) from operations	(172,082)	365,883	(61,372)
Other income (expense):			
Investment income.	30,562	52,013	30,397
Interest expense	(44,990)	(48,768)	(44,789)
Gain (loss) on investments	16,540	192	(210)
Loss on early retirement of debt.	—	(21,865)	—
Other expenses.	(62)	(686)	(182)
Income (loss) before income tax benefit (expense).	(170,032)	346,769	(76,156)
Income tax benefit (expense)	(316,734)	(43,507)	291,141
Net income (loss)	(486,766)	303,262	214,985
Net (income) loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	35,480	(9,116)	58,756
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	\$(451,286)	\$ 294,146	\$273,741
Basic net income (loss) per share	\$ (3.23)	\$ 2.12	\$ 2.09
Shares used in computing basic net income (loss) per share	139,612	139,998	132,320
Diluted net income (loss) per share	\$ (3.23)	\$ 2.08	\$ 2.07
Shares used in computing diluted net income (loss) per share	139,612	142,872	134,056

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME (LOSS)
(In thousands)

	Year Ended December 31,		
	2020	2019	2018
Net income (loss)	\$(486,766)	\$303,262	\$214,985
Unrealized gains (losses) on investments, net of tax	3,729	6,633	(280)
Currency translation adjustment	617	93	23
Adjustments to other comprehensive loss from purchase of noncontrolling interest of Akcea Therapeutics, Inc.	<u>(127)</u>	<u>—</u>	<u>—</u>
Comprehensive income (loss)	(482,547)	309,988	214,728
Comprehensive income (loss) attributable to noncontrolling interest in Akcea Therapeutics, Inc.	<u>(35,480)</u>	<u>9,118</u>	<u>(58,781)</u>
Comprehensive income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	<u><u>\$(447,067)</u></u>	<u><u>\$300,870</u></u>	<u><u>\$273,509</u></u>

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2020, 2019 and 2018
(In thousands)

Description	Common Stock		Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
	Shares	Amount						
Balance at December 31, 2017	124,976	\$125	\$1,553,681	\$(31,759)	\$(1,241,034)	\$ 281,013	\$ 84,267	\$ 365,280
Net income	—	—	—	—	273,741	273,741	—	273,741
Change in unrealized losses, net of tax	—	—	—	(280)	—	(280)	—	(280)
Foreign currency translation	—	—	—	23	—	23	—	23
Biogen stock purchase	11,502	11	447,954	—	—	447,965	—	447,965
Issuance of common stock in connection with employee stock plans	1,451	2	27,898	—	—	27,900	—	27,900
Stock-based compensation expense	—	—	131,312	—	—	131,312	—	131,312
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(113,595)	—	—	(113,595)	54,814	(58,781)
Balance at December 31, 2018	<u>137,929</u>	<u>\$138</u>	<u>\$2,047,250</u>	<u>\$(32,016)</u>	<u>\$ (967,293)</u>	<u>\$1,048,079</u>	<u>\$ 139,081</u>	<u>\$1,187,160</u>
Net income	—	—	—	—	294,146	294,146	—	294,146
Change in unrealized gain, net of tax	—	—	—	6,633	—	6,633	—	6,633
Foreign currency translation	—	—	—	93	—	93	—	93
Issuance of common stock in connection with employee stock plans	3,100	3	119,654	—	—	119,657	—	119,657
1 percent convertible senior notes retirement, equity portion, net of tax	—	—	(77,331)	—	—	(77,331)	—	(77,331)
0.125 percent convertible senior notes, equity portion, net of issuance costs and tax	—	—	81,877	—	—	81,877	—	81,877
Issuance of warrants	—	—	56,110	—	—	56,110	—	56,110
Purchase of note hedges, net of tax	—	—	(85,860)	—	—	(85,860)	—	(85,860)
Repurchases and retirements of common stock	(535)	(1)	—	—	(34,387)	(34,388)	—	(34,388)
Stock-based compensation expense	—	—	146,574	—	—	146,574	—	146,574
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(154)	—	(19,242)	—	—	(19,242)	—	(19,242)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(65,254)	—	—	(65,254)	74,372	9,118
Balance at December 31, 2019	<u>140,340</u>	<u>\$140</u>	<u>\$2,203,778</u>	<u>\$(25,290)</u>	<u>\$ (707,534)</u>	<u>\$1,471,094</u>	<u>\$ 213,453</u>	<u>\$1,684,547</u>
Net loss	—	—	—	—	(451,286)	(451,286)	—	(451,286)
Change in unrealized gains, net of tax	—	—	—	3,729	—	3,729	—	3,729
Foreign currency translation	—	—	—	617	—	617	—	617
Issuance of common stock in connection with employee stock plans	1,721	1	52,033	—	—	52,034	—	52,034
Purchase of noncontrolling interest of Akcea Therapeutics, Inc., including cash payments for cancellation of Akcea Therapeutics, Inc. equity awards	—	—	(324,022)	301	—	(323,721)	(220,965)	(544,686)
Repurchases and retirement of common stock	(1,478)	(1)	—	—	(90,548)	(90,549)	—	(90,549)
Stock-based compensation expense	—	—	230,117	—	—	230,117	—	230,117
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(217)	—	(13,410)	—	—	(13,410)	—	(13,410)
Deferred tax liability adjustment due to purchase of noncontrolling interest of Akcea Therapeutics, Inc.	—	—	7,714	—	—	7,714	—	7,714
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(42,564)	(428)	—	(42,992)	7,512	(35,480)
Balance at December 31, 2020	<u>140,366</u>	<u>\$140</u>	<u>\$2,113,646</u>	<u>\$(21,071)</u>	<u>\$(1,249,368)</u>	<u>\$ 843,347</u>	<u>\$ —</u>	<u>\$ 843,347</u>

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,		
	2020	2019	2018
Operating activities:			
Net income (loss)	\$ (486,766)	\$ 303,262	\$ 214,985
Adjustments to reconcile net income (loss) to net cash provided by operating activities:			
Depreciation	13,365	12,540	10,706
Amortization of right-of-use operating lease assets	1,731	1,542	—
Amortization of patents	2,064	1,912	1,822
Amortization of premium (discount) on investments, net	11,521	(7,485)	(1,013)
Amortization of debt issuance costs	2,578	1,942	1,810
Amortization of convertible senior notes discount	36,157	37,338	33,363
Stock-based compensation expense	230,117	146,574	131,312
Loss on early retirement of debt	—	21,865	—
(Gain) loss on investments	(16,540)	(192)	210
Deferred income taxes, including changes in valuation allowance ..	313,272	(7,096)	(290,516)
Non-cash losses related to patents	1,948	2,226	802
Changes in operating assets and liabilities:			
Contracts receivable	(13,170)	(47,674)	47,595
Inventories	(1,261)	(5,411)	1,400
Other current and long-term assets	(9,975)	(44,659)	(29,348)
Long-term income tax receivable	—	8,418	(223)
Accounts payable	(2,755)	(16,343)	(655)
Income taxes	(31,279)	31,656	(710)
Accrued compensation	28,371	8,089	4,117
Accrued liabilities and deferred rent	32,424	16,406	(17,005)
Deferred contract revenue	(75,910)	(119,283)	494,254
Net cash provided by operating activities	<u>35,892</u>	<u>345,627</u>	<u>602,906</u>
Investing activities:			
Purchases of short-term investments	(1,570,410)	(1,946,726)	(1,794,735)
Proceeds from the sale of short-term investments	1,885,935	1,951,734	882,824
Purchases of property, plant and equipment	(35,120)	(30,905)	(13,608)
Acquisition of licenses and other assets, net	(5,928)	(5,377)	(4,044)
Purchase of strategic investments	—	(10,000)	—
Net cash provided by (used in) investing activities	<u>274,477</u>	<u>(41,274)</u>	<u>(929,563)</u>

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,		
	2020	2019	2018
Financing activities:			
Proceeds from equity, net.	52,036	119,657	27,900
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(13,411)	(19,242)	—
Proceeds from the issuance of 0.125 percent convertible senior notes	—	109,500	—
0.125 percent convertible senior notes issuance costs	—	(10,428)	—
Proceeds from issuance of warrants.	—	56,110	—
Purchase of note hedges.	—	(108,684)	—
Repurchases and retirements of common stock	(90,548)	(34,392)	—
Purchase of noncontrolling interest of Akcea Therapeutics, Inc., including cash payments for cancellation of Akcea Therapeutics, Inc. equity awards.	(544,686)	—	—
Principal payments on line of credit	—	(12,500)	—
Proceeds from the issuance of common stock to Biogen.	—	—	447,965
Net cash (used in) provided by financing activities	<u>(596,609)</u>	<u>100,021</u>	<u>475,865</u>
Effects of exchange rates on cash	617	93	(18)
Net (decrease) increase in cash and cash equivalents.	(285,623)	404,467	149,190
Cash and cash equivalents at beginning of year.	<u>683,287</u>	<u>278,820</u>	<u>129,630</u>
Cash and cash equivalents at end of year.	<u>\$ 397,664</u>	<u>\$ 683,287</u>	<u>\$278,820</u>
Supplemental disclosures of cash flow information:			
Interest paid	\$ 6,247	\$ 9,870	\$ 9,592
Income taxes paid.	\$ 25,855	\$ 9,041	\$ —
Supplemental disclosures of non-cash investing and financing activities:			
Right-of-use assets obtained in exchange for lease liabilities	\$ 2,149	\$ 14,178	\$ —
Amounts accrued for capital and patent expenditures	\$ 4,059	\$ 3,126	\$ 4,428
Purchases of property, plant and equipment included in long-term obligations.	\$ —	\$ —	\$ 3,350
0.125 percent convertible senior notes principal issued related to our December 2019 debt exchange/issuance.	\$ —	\$ 439,326	\$ —
1 percent convertible senior notes principal extinguished related to our December 2019 debt exchange	\$ —	\$ 375,590	\$ —

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Organization and Significant Accounting Policies

Basis of Presentation

In our consolidated financial statements we included the accounts of Ionis Pharmaceuticals, Inc. and the consolidated results of our subsidiary, Akcea Therapeutics, Inc. and its wholly owned subsidiaries (“we”, “us” or “our”). We formed Akcea in December 2014. In July 2017, Akcea completed an initial public offering, or IPO. Prior to Akcea’s IPO in July 2017, we owned 100 percent of Akcea. In October 2020, we acquired the shares of Akcea’s common stock we did not own. We will refer to this transaction as the Akcea Acquisition throughout the remainder of this document. See Note 7, *Akcea Acquisition*, in the Notes to the Consolidated Financial Statements for further details. We reflected changes in our ownership percentage in our financial statements as an adjustment to noncontrolling interest in the period the change occurred.

Organization and Business Activity

We incorporated in California on January 10, 1989. In conjunction with our IPO, we reorganized as a Delaware corporation in April 1991. We were organized principally to develop human therapeutic medicines using antisense technology. In December 2015, we changed our name from Isis Pharmaceuticals, Inc. to Ionis Pharmaceuticals, Inc.

Basic and Diluted Net Income (Loss) per Share

Basic net income (loss) per share

We compute basic net income (loss) per share by dividing the total net income (loss) attributable to our common stockholders by our weighted-average number of common shares outstanding during the period.

The calculation of total net income (loss) attributable to our common stockholders for each year considered our net income (loss) for Ionis on a stand-alone basis plus our share of Akcea’s net income (loss) for the period. To calculate the portion of Akcea’s net income (loss) attributable to our ownership for each year, we multiplied Akcea’s income (loss) per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net income (loss) available to Ionis common stockholders for the calculation of net income (loss) per share is different than net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders in our consolidated statements of operations for each year.

Our basic net income (loss) per share was calculated as follows (in thousands, except per share amounts):

<u>Year Ended December 31, 2020</u>	<u>Weighted Average Shares Owned in Akcea</u>	<u>Akcea’s Net Loss Per Share</u>	<u>Basic Net Loss Per Share Calculation</u>
Akcea’s net loss in the pre-acquisition period attributable to our ownership	77,095	\$(1.45)	\$(111,775)
Akcea’s net loss in the post-acquisition period attributable to our ownership			(85,987)
Akcea’s total net loss attributable to our ownership			\$(197,762)
Ionis’ stand-alone net loss.			(253,725)
Net loss available to Ionis common stockholders			\$(451,487)
Weighted average shares outstanding.			139,612
Basic net loss per share			\$ (3.23)
<u>Year Ended December 31, 2019</u>	<u>Weighted Average Shares Owned in Akcea</u>	<u>Akcea’s Net Income Per Share</u>	<u>Basic Net Income Per Share Calculation</u>
Common shares.	70,100	\$0.49	\$ 34,073
Akcea’s net income attributable to our ownership			\$ 34,073
Ionis’ stand-alone net income.			262,490
Net income available to Ionis common stockholders			\$296,563
Weighted average shares outstanding.			139,998
Basic net income per share.			\$ 2.12

Year Ended December 31, 2018	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Income Per Share Calculation
Common shares	59,812	\$(2.74)	\$(163,938)
Akcea's net loss attributable to our ownership			\$(163,938)
Ionis' stand-alone net income			<u>440,806</u>
Net income available to Ionis common stockholders			\$ 276,868
Weighted average shares outstanding			<u>132,320</u>
Basic net income per share			<u>\$ 2.09</u>

Diluted net income per share

For the year ended December 31, 2020, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 0.125 percent convertible senior notes;
- 1 percent convertible senior notes;
- Dilutive stock options;
- Unvested restricted stock units, or RSUs; and
- Employee Stock Purchase Plan, or ESPP.

For the years ended December 31, 2019 and 2018, we had net income available to Ionis common stockholders. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during each period. We calculated our diluted net income per share as follows (in thousands except per share amounts):

Year Ended December 31, 2019	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	\$296,563	139,998	<u>\$2.12</u>
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	2,090	
Shares issuable upon restricted stock award issuance	—	766	
Shares issuable related to our ESPP	—	18	
	<u>\$296,563</u>	<u>142,872</u>	<u>\$2.08</u>
Year Ended December 31, 2018	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	\$276,868	132,320	<u>\$2.09</u>
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,216	
Shares issuable upon restricted stock award issuance	—	514	
Shares issuable related to our ESPP	—	6	
	<u>\$276,868</u>	<u>134,056</u>	<u>\$2.07</u>

For each year presented, the calculation excluded our convertible senior notes because the effect on diluted earnings per share was anti-dilutive.

Revenue Recognition

Our Revenue Sources

We generally recognize revenue when we have satisfied all contractual obligations and are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue. In the instances in which we have received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on our consolidated balance sheet.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We earn commercial revenue primarily in the form of royalty payments on net sales of SPINRAZA. We will also recognize as commercial revenue sales milestone payments and royalties we earn under our other partnerships.

Commercial Revenue: Product sales, net

We added product sales from TEGSEDI to our commercial revenue in the fourth quarter of 2018 and we added product sales from WAYLIVRA to our commercial revenue in the third quarter of 2019. In the U.S., we distribute TEGSEDI through an exclusive distribution agreement with a third-party logistics company, or 3PL, that takes title to TEGSEDI. The 3PL is our sole customer in the U.S. The 3PL then distributes TEGSEDI to a specialty pharmacy and a specialty distributor, which we collectively refer to as wholesalers, who then distribute TEGSEDI to health care providers and patients.

In Europe, through 2020 we sold TEGSEDI and WAYLIVRA to hospitals and pharmacies using 3PLs as distributors. Beginning in 2021, we are commercializing TEGSEDI and WAYLIVRA in Europe through a distribution agreement with Swedish Orphan Biovitrum AB, or Sobi, an international biopharmaceutical company that focuses on rare diseases. Under the terms of this agreement, we retained the marketing authorization for both medicines in Europe.

In Latin America beginning in 2020, we sold TEGSEDI and WAYLIVRA to our partner, PTC Therapeutics. Under our collaboration agreement with PTC, PTC is commercializing TEGSEDI and WAYLIVRA in Latin America and Caribbean countries.

Research and development revenue under collaborative agreements

We often enter into collaboration agreements to license and sell our technology on an exclusive or non-exclusive basis. Our collaboration agreements typically contain multiple elements, or performance obligations, including technology licenses or options to obtain technology licenses, research and development, or R&D, services, and manufacturing services.

We provide details about our collaboration agreements in Note 6, *Collaborative Arrangements and Licensing Agreements*. Under each collaboration note we discuss our specific revenue recognition conclusions, including our significant performance obligations under each collaboration.

Steps to Recognize Revenue

We use a five-step process to determine the amount of revenue we should recognize and when we should recognize it. The five step process is as follows:

1. Identify the contract

Accounting rules require us to first determine if we have a contract with our partner, including confirming that we have met each of the following criteria:

- We and our partner approved the contract and we are both committed to perform our obligations;
- We have identified our rights, our partner's rights and the payment terms;
- We have concluded that the contract has commercial substance, meaning that the risk, timing, or amount of our future cash flows is expected to change as a result of the contract; and
- We believe collectability of the consideration is probable.

2. Identify the performance obligations

We next identify our performance obligations, which represent the distinct goods and services we are required to provide under the contract. We typically have only one performance obligation at the inception of a contract, which is to perform R&D services.

Often we enter into a collaboration agreement in which we provide our partner with an option to license a medicine in the future. We may also provide our partner with an option to request that we provide additional goods or services in the future, such as active pharmaceutical ingredient, or API. We evaluate whether these options are

material rights at the inception of the agreement. If we determine an option is a material right, we will consider the option a separate performance obligation. Historically, we have concluded that the options we grant to license a medicine in the future or to provide additional goods and services as requested by our partner are not material rights because these items are contingent upon future events that may not occur and are not priced at a significant discount. When a partner exercises its option to license a medicine or requests additional goods or services, then we identify a new performance obligation for that item.

In some cases, we deliver a license at the start of an agreement. If we determine that our partner has full use of the license and we do not have any additional material performance obligations related to the license after delivery, then we consider the license to be a separate performance obligation.

3. *Determine the transaction price*

We then determine the transaction price by reviewing the amount of consideration we are eligible to earn under the collaboration agreement, including any variable consideration. Under our collaboration agreements, consideration typically includes fixed consideration in the form of an upfront payment and variable consideration in the form of potential milestone payments, license fees and royalties. At the start of an agreement, our transaction price usually consists of only the upfront payment. We do not typically include any payments we may receive in the future in our initial transaction price because the payments are not probable and are contingent on certain future events. We reassess the total transaction price at each reporting period to determine if we should include additional payments in the transaction price.

Milestone payments are our most common type of variable consideration. We recognize milestone payments using the most likely amount method because we will either receive the milestone payment or we will not, which makes the potential milestone payment a binary event. The most likely amount method requires us to determine the likelihood of earning the milestone payment. We include a milestone payment in the transaction price once it is probable we will achieve the milestone event. Most often, we do not consider our milestone payments probable until we or our partner achieve the milestone event because the majority of our milestone payments are contingent upon events that are not within our control and/ or are usually based on scientific progress which is inherently uncertain. For example, in the fourth quarter of 2020, we earned a \$20 million milestone payment from AstraZeneca when AstraZeneca initiated a Phase 2b study for ION449, our medicine in development targeting PCSK9 to lower LDL-cholesterol. We did not consider the milestone payment probable until AstraZeneca achieved the milestone event because advancing ION449 was contingent on AstraZeneca initiating a Phase 2b study and was not within our control. We recognized the milestone payment in full in the period the milestone event was achieved because we did not have any remaining performance obligations related to the milestone payment.

4. *Allocate the transaction price*

Next, we allocate the transaction price to each of our performance obligations. When we have to allocate the transaction price to more than one performance obligation, we make estimates of the relative stand-alone selling price of each performance obligation because we do not typically sell our goods or services on a stand-alone basis. We then allocate the transaction price to each performance obligation based on the relative stand-alone selling price. We do not reallocate the transaction price after the start of an agreement to reflect subsequent changes in stand-alone selling prices.

We may engage a third party, independent valuation specialist to assist us with determining a stand-alone selling price for collaborations in which we deliver a license at the start of an agreement. We estimate the stand-alone selling price of these licenses using valuation methodologies, such as the relief from royalty method. Under this method, we estimate the amount of income, net of taxes, for the license. We then discount the projected income to present value. The significant inputs we use to determine the projected income of a license could include:

- Estimated future product sales;
- Estimated royalties we may receive from future product sales;
- Estimated contractual milestone payments we may receive;
- Expenses we expect to incur;
- Estimated income taxes; and
- A discount rate.

We typically estimate the selling price of R&D services by using our internal estimates of the cost to perform the specific services. The significant inputs we use to determine the selling price of our R&D services include:

- The number of internal hours we estimate we will spend performing these services;
- The estimated cost of work we will perform;
- The estimated cost of work that we will contract with third parties to perform; and
- The estimated cost of API we will use.

For purposes of determining the stand-alone selling price of the R&D services we perform and the API we will deliver, accounting guidance requires us to include a markup for a reasonable profit margin.

5. *Recognize revenue*

We recognize revenue in one of two ways, over time or at a point in time. We recognize revenue over time when we are executing on our performance obligation over time and our partner receives benefit over time. For example, we recognize revenue over time when we provide R&D services. We recognize revenue at a point in time when our partner receives full use of an item at a specific point in time. For example, we recognize revenue at a point in time when we deliver a license or API to a partner.

For R&D services that we recognize over time, we measure our progress using an input method. The input methods we use are based on the effort we expend or costs we incur toward the satisfaction of our performance obligation. We estimate the amount of effort we expend, including the time we estimate it will take us to complete the activities, or costs we incur in a given period, relative to the estimated total effort or costs to satisfy the performance obligation. This results in a percentage that we multiply by the transaction price to determine the amount of revenue we recognize each period. This approach requires us to make numerous estimates and use significant judgement. If our estimates or judgements change over the course of the collaboration, they may affect the timing and amount of revenue that we recognize in the current and future periods. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion of the cumulative catch up adjustment we made.

The following are examples of when we typically recognize revenue based on the types of payments we receive.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We recognize royalty revenue, including royalties from SPINRAZA sales, in the period in which the counterparty sells the related product and recognizes the related revenue, which in certain cases may require us to estimate our royalty revenue.

Commercial Revenue: Product sales, net

We recognize product sales in the period when our customer obtains control of our products, which occurs at a point in time upon transfer of title to the customer. We classify payments to customers or other parties in the distribution channel for services that are distinct and priced at fair value as selling, general and administrative, or SG&A, expenses in our consolidated statements of operations. Otherwise, payments to customers or other parties in the distribution channel that do not meet those criteria are classified as a reduction of revenue, as discussed further below. We exclude from revenues taxes collected from customers relating to product sales and remitted to governmental authorities.

Reserves for Product sales

We record product sales at our net sales price, or transaction price. We include in our transaction price estimated reserves for discounts, returns, chargebacks, rebates and other allowances that we offer within contracts between us and our customers, wholesalers, health care providers and other indirect customers. We estimate our reserves using the amounts we have earned or what we can claim on the associated sales. We classify our reserves as a reduction of accounts receivable when we are not required to make a payment or as a current liability when we are required to make a payment. In certain cases, our estimates include a range of possible outcomes that are probability weighted for relevant factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. Overall, our reserves reflect our best estimates under the terms of our respective contracts. When calculating our reserves and related

product sales, we only recognize amounts to the extent that we consider it probable that we would not have to reverse in a future period a significant amount of the cumulative sales we previously recognized. The actual amounts we receive may ultimately differ from our reserve estimates. If actual amounts in the future vary from our estimates, we will adjust these estimates, which would affect our net product sales in the respective period.

The following are the components of variable consideration related to product sales:

Chargebacks: In the U.S., 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 our U.S. customer. Our U.S. customer charges us for the difference between what it pays for the product and the selling price to the qualified healthcare providers. We also estimate the amount of chargebacks related to our estimated product remaining in the distribution channel at the end of the reporting period that we expect our customer to sell to healthcare providers in future periods. We record these reserves as a reduction to contracts receivable on our consolidated balance sheet.

Government rebates: We are subject to discount obligations under government programs, including Medicaid and Medicare programs in the U.S. and we record reserves for government rebates based on statutory discount rates and estimated utilization. We estimate Medicaid and Medicare rebates based on a range of possible outcomes that are probability weighted for the estimated payer mix. We record these reserves as an accrued liability on our consolidated balance sheet with a corresponding offset reducing our product sales in the same period we recognize the related sale. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program. On a quarterly basis, we update our estimates and record any adjustments in the period that we identify the adjustments.

Managed care rebates: We are subject to rebates in connection with agreements with certain contracted commercial payers. We record these rebates as a liability on our consolidated balance sheet in the same period we recognize the related revenue. We estimate our managed care rebates based on our estimated payer mix and the applicable contractual rebate rate.

Trade discounts: We provide customary invoice discounts on product sales to our U.S. customer for prompt payment. We record this discount as a reduction of product sales in the period in which we recognize the related product revenue.

Distribution services: We receive and pay for various distribution services from our U.S. and European customers (prior to our agreement with Sobi) and wholesalers in the U.S. We classify the costs for services we receive that are either not distinct from the sale of the product or for which we cannot reasonably estimate the fair value as a reduction of product sales. To the extent that the services we receive are distinct from the sale of the product, we classify the costs for such services as SG&A expenses.

Product returns: Our U.S. customer has return rights and the wholesalers have limited return rights primarily related to the product's expiration date. We estimate the amount of product sales that our customer may return. We record our return estimate as an accrued refund liability on our consolidated balance sheet with a corresponding offset reducing our product sales in the same period we recognize the related sale. Based on our distribution model for product sales, contractual inventory limits with our customer and wholesalers and the price of the product, we have had minimal returns to date and we believe we will continue to have minimal returns in the U.S. Our European customers generally only take title to the product after they receive an order and therefore they do not maintain excess inventory levels of our products. Accordingly, we have limited return risk in Europe and we do not estimate returns in Europe.

Research and development revenue under collaboration agreements:

Upfront payments

When we enter into a collaboration agreement with an upfront payment, we typically record the entire upfront payment as deferred revenue if our only performance obligation is for R&D services we will provide in the future. We amortize the upfront payment into revenue as we perform the R&D services. For example, under our collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases, we received a \$75 million upfront payment in the fourth quarter of 2018. We allocated the upfront payment to our single performance obligation, R&D services. We are amortizing the \$75 million upfront payment using an input method over the estimated period of time we are providing R&D services.

Milestone payments

We are required to include additional consideration in the transaction price when it is probable. We typically include milestone payments for R&D services in the transaction price when they are achieved. We include these milestone payments when they are achieved because typically there is considerable uncertainty in the research and development processes that trigger these payments. Similarly, we include approval milestone payments in the transaction price once the medicine is approved by the applicable regulatory agency. We will recognize sales-based milestone payments in the period in which we achieve the milestone under the sales-based royalty exception allowed under accounting rules.

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, in the fourth quarter of 2020, we achieved a \$7.5 million milestone payment from Biogen when we advanced a target under our 2018 strategic collaboration. We added this payment to the transaction price and allocated it to our R&D services performance obligation. We are recognizing revenue related to this milestone payment over our estimated period of performance.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event and we do not have a performance obligation. For example, in the third quarter of 2020, we recognized \$18 million in milestone payments when Biogen initiated a Phase 1/2 trial for ION464, our medicine in development targeting alpha-synuclein to treat patients with multiple system atrophy. We concluded that the milestone payments were not related to our R&D services performance obligation. Therefore, we recognized the milestone payments in full in the third quarter of 2020.

License fees

We generally recognize as revenue the total amount we determine to be the relative stand-alone selling price of a license when we deliver the license to our partner. This is because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery. For example, in the fourth quarter of 2020, we earned a \$30 million license fee from AstraZeneca when AstraZeneca licensed ION455, an investigational medicine in development to treat nonalcoholic steatohepatitis, or NASH.

Sublicense fees

We recognize sublicense fee revenue in the period in which a party, who has already licensed our technology, further licenses the technology to another party because we do not have any performance obligations related to the sublicense. For example, in the fourth quarter of 2020, we earned a \$41.2 million sublicense fee from Alnylam Pharmaceuticals for its sublicense of our technology to Sanofi Genzyme.

Amendments to Agreements

From time to time we amend our collaboration agreements. When this occurs, we are required to assess the following items to determine the accounting for the amendment:

- 1) If the additional goods and/or services are distinct from the other performance obligations in the original agreement; and
- 2) If the goods and/or services are at a stand-alone selling price.

If we conclude the goods and/or services in the amendment are distinct from the performance obligations in the original agreement and at a stand-alone selling price, we account for the amendment as a separate agreement. If we conclude the goods and/or services are not distinct and are sold at a stand-alone selling price, we then assess whether the remaining goods or services are distinct from those already provided. If the goods and/or services are distinct from what we have already provided, then we allocate the remaining transaction price from the original agreement and the additional transaction price from the amendment to the remaining goods and/or services. If the goods and/or services are not distinct from what we have already provided, we update the transaction price for our single performance obligation and recognize any change in our estimated revenue as a cumulative adjustment.

For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI_{Rx} for the prevention of thrombosis. As part of the agreement, Bayer paid us a \$100 million upfront payment. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI_{Rx} in people with end-stage renal disease on hemodialysis and for providing an initial supply of API. In February 2017,

we amended our agreement with Bayer to advance IONIS-FXI_{Rx} and to initiate development of IONIS-FXI-L_{Rx}, which Bayer licensed. As part of the 2017 amendment, Bayer paid us \$75 million. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI_{Rx} and IONIS-FXI-L_{Rx}. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of IONIS-FXI-L_{Rx}, to provide R&D services and to deliver API. We allocated the \$75 million transaction price to these performance obligations. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, in our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2019 for further discussion of the Bayer collaboration.

Multiple agreements

From time to time, we may enter into separate agreements at or near the same time with the same partner. We evaluate such agreements to determine whether we should account for them individually as distinct arrangements or whether the separate agreements should be combined and accounted for together. We evaluate the following to determine the accounting for the agreements:

- Whether the agreements were negotiated together with a single objective;
- Whether the amount of consideration in one contract depends on the price or performance of the other agreement; or
- Whether the goods and/or services promised under the agreements are a single performance obligation.

Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that accounting guidance requires us to account for them as a combined arrangement.

For example, in the second quarter of 2018, we entered into two separate agreements with Biogen at the same time: a new strategic neurology collaboration agreement and a stock purchase agreement, or SPA. We evaluated the Biogen agreements to determine whether we should treat the agreements separately or combine them. We considered that the agreements were negotiated concurrently and in contemplation of one another. Based on these facts and circumstances, we concluded that we should evaluate the provisions of the agreements on a combined basis.

Contracts Receivable

Our contracts receivable balance represents the amounts we have billed our partners or customers and that are due to us unconditionally for goods we have delivered or services we have performed. When we bill our partners or customers with payment terms based on the passage of time, we consider the contracts receivable to be unconditional. We typically receive payment within one quarter of billing our partner or customer.

Unbilled SPINRAZA Royalties

Our unbilled SPINRAZA royalties represent our right to receive consideration from Biogen in advance of when we are eligible to bill Biogen for SPINRAZA royalties. We include these unbilled amounts in other current assets on our consolidated balance sheet.

Deferred Revenue

We are often entitled to bill our customers and receive payment from our customers in advance of our obligation to provide services or transfer goods to our partners. In these instances, we include the amounts in deferred revenue on our consolidated balance sheet. During the years ended December 31, 2020 and 2019, we recognized \$100.4 million and \$159.5 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. For further discussion, refer to our revenue recognition policy above.

Cost of Products Sold

Our cost of products sold includes manufacturing costs, transportation and freight costs and indirect overhead costs associated with the manufacturing and distribution of our products. We also may include certain period costs related to manufacturing services and inventory adjustments in cost of products sold. Prior to obtaining regulatory approval of TEGSEDI in July 2018 and WAYLIVRA in May 2019, we expensed as research and development expenses a significant portion of the costs we incurred to produce the initial commercial launch supply for each medicine.

Research, Development and Patent Expenses

Our research and development expenses include wages, benefits, facilities, supplies, external services, clinical trial and manufacturing costs and other expenses that are directly related to our research and development operations. We expense research and development costs as we incur them. When we make payments for research and development services prior to the services being rendered, we record those amounts as prepaid assets on our consolidated balance sheet and we expense them as the services are provided. For the years ended December 31, 2020, 2019 and 2018, research and development expenses were \$531.0 million, \$461.5 million and \$411.9 million, respectively. A portion of the costs included in research and development expenses are costs associated with our partner agreements. For the years ended December 31, 2020, 2019 and 2018, research and development costs of approximately \$49.8 million, \$83.2 million and \$58.7 million, respectively, were related to our partner agreements.

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We amortize patent costs over the useful life of the patent, beginning with the date the U.S. Patent and Trademark Office, or foreign equivalent, issues the patent. The weighted average remaining amortizable life of our issued patents was 10.3 years at December 31, 2020.

The cost of our patents capitalized on our consolidated balance sheet at December 31, 2020 and 2019 was \$37.0 million and \$34.0 million, respectively. Accumulated amortization related to patents was \$9.1 million and \$8.3 million at December 31, 2020 and 2019, respectively.

Based on our existing patents, we estimate amortization expense related to patents in each of the next five years to be the following:

<u>Year Ending December 31,</u>	<u>Amortization (in millions)</u>
2021.....	\$2.1
2022.....	\$2.0
2023.....	\$1.9
2024.....	\$1.7
2025.....	\$1.6

We review our capitalized patent costs regularly to ensure that they include costs for patents and patent applications that have future value. When we identify patents and patent applications that we are not actively pursuing, we write off any associated costs. In 2020, 2019 and 2018, patent expenses were \$4.1 million, \$4.2 million and \$2.6 million, respectively, and included non-cash charges related to the write-down of our patent costs to their estimated net realizable values of \$1.9 million, \$2.2 million and \$0.8 million, respectively.

Accrued Liabilities

Our accrued liabilities consisted of the following (in thousands):

	<u>December 31,</u>	
	<u>2020</u>	<u>2019</u>
Clinical expenses.....	\$39,477	\$24,461
In-licensing expenses.....	8,264	10,289
Commercial expenses.....	11,559	6,020
Other miscellaneous expenses.....	30,861	25,999
Total accrued liabilities.....	<u>\$90,161</u>	<u>\$66,769</u>

Noncontrolling Interest in Akcea Therapeutics, Inc.

Since Akcea's IPO in July 2017 and prior to the Akcea Acquisition in October 2020, the shares of Akcea's common stock third parties owned represented an interest in Akcea's equity that we did not control. During this period our ownership ranged from 68 percent to 77 percent. However, as we maintained overall control of Akcea through our voting interest, we reflected the assets, liabilities and results of operations of Akcea in our consolidated financial statements. Since Akcea's IPO in July 2017 and through the closing of the Akcea Acquisition, we reflected the noncontrolling interest attributable to other owners of Akcea's common stock on a separate line on our statement

of operations and a separate line within stockholders' equity in our consolidated balance sheet. In addition, through the closing of the Akcea Acquisition, we recorded a noncontrolling interest adjustment to account for the stock options Akcea granted, which if exercised, would have diluted our ownership in Akcea. This adjustment was a reclassification within stockholders' equity from additional paid-in capital to noncontrolling interest in Akcea equal to the amount of stock-based compensation expense Akcea had recognized. Additionally, we reflected changes in our ownership percentage in our financial statements as an adjustment to noncontrolling interest in the period the change occurred.

Concentration of Credit Risk

Financial instruments that potentially subject us to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. We place our cash equivalents and short-term investments with reputable financial institutions. We primarily invest our excess cash in commercial paper and debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or S&P, or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

Cash, Cash Equivalents and Investments

We consider all liquid investments with maturities of three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months from date of purchase. We classify our short-term debt investments as "available-for-sale" and carry them at fair market value based upon prices on the last day of the fiscal period for identical or similar items. We record unrealized gains and losses on debt securities as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments in our consolidated statement of operations. We use the specific identification method to determine the cost of securities sold.

We also have equity investments of less than 20 percent ownership in publicly and privately held biotechnology companies that we received as part of a technology license or partner agreement. At December 31, 2020, we held equity investments in two publicly held companies, ProQR Therapeutics N.V., or ProQR, and Antisense Therapeutics Limited, or ATL. We also held equity investments in seven privately-held companies, Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, Seventh Sense Biosystems and Suzhou-Ribo Life Science Co, Ltd.

We are required to measure and record our equity investments at fair value and to recognize the changes in fair value in our consolidated statement of operations. We account for our equity investments in privately held companies at their cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer. For example, during the second and fourth quarters of 2020, we revalued our investments in three privately held companies, Dynacure, Suzhou-Ribo and Aro Biotherapeutics because the companies sold additional equity securities that were similar to the equity we own. These observable price changes resulted in us recognizing a \$6.3 million gain on our investment in Dynacure, a \$3.0 million gain on our investment in Suzhou-Ribo and a \$5.5 million gain on our investment in Aro Biotherapeutics in our consolidated statement of operations during 2020 because the sales were at higher prices compared to our recorded value.

Inventory Valuation

We reflect our inventory on our consolidated balance sheet at the lower of cost or net realizable value under the first-in, first-out method, or FIFO. We capitalize the costs of raw materials that we purchase for use in producing our medicines because until we use these raw materials, they have alternative future uses, which we refer to as clinical raw materials. We include in inventory raw material costs for medicines that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We can use each of our raw materials in multiple products and, as a result, each raw material has future economic value independent of the development status of any single medicine. For example, if one of our medicines failed, we could use the raw materials for that medicine to manufacture our other medicines. We expense these costs as R&D expenses when we begin to manufacture API for a particular medicine if the medicine has not been approved for marketing by a regulatory agency.

We obtained the first regulatory approval for TEGSEDI in July 2018 and for WAYLIVRA in May 2019. At December 31, 2020, our physical inventory for TEGSEDI and WAYLIVRA included API that we produced prior to when we obtained regulatory approval. As such, this API has no cost basis as we had previously expensed the costs as R&D expenses.

We review our inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value based on forecasted demand compared to quantities on hand. We consider several factors in estimating the net realizable value, including shelf life of our inventory, alternative uses for our medicines in development and historical write-offs. We recorded an insignificant amount of inventory write-offs during the years ended December 31, 2020 and 2019. We did not record any inventory write-offs for the year ended December 31, 2018.

Our inventory consisted of the following (in thousands):

	<u>December 31,</u>	
	<u>2020</u>	<u>2019</u>
Raw materials:		
Raw materials- clinical	\$ 9,206	\$ 9,363
Raw materials- commercial	<u>7,502</u>	<u>6,520</u>
Total raw materials	16,708	15,883
Work in process	2,252	2,039
Finished goods	<u>3,005</u>	<u>258</u>
Total inventory	<u>\$21,965</u>	<u>\$18,180</u>

Property, Plant and Equipment

We carry our property, plant and equipment at cost and depreciate it on the straight-line method over its estimated useful life, which consists of the following (in thousands):

	<u>Estimated Useful Lives (in years)</u>	<u>December 31,</u>	
		<u>2020</u>	<u>2019</u>
Computer software, laboratory, manufacturing and other equipment	3 to 10	\$ 68,990	\$ 60,965
Building, building improvements and building systems	15 to 40	137,879	119,830
Land improvements	20	8,391	2,853
Leasehold improvements	5 to 15	17,263	13,600
Furniture and fixtures	5 to 10	<u>12,871</u>	<u>7,354</u>
		245,394	204,602
Less accumulated depreciation		<u>(87,379)</u>	<u>(74,013)</u>
		158,015	130,589
Land		<u>23,062</u>	<u>23,062</u>
Total		<u>\$181,077</u>	<u>\$153,651</u>

We depreciate our leasehold improvements using the shorter of the estimated useful life or remaining lease term.

Fair Value of Financial Instruments

We have estimated the fair value of our financial instruments. The amounts reported for cash, accounts receivable, accounts payable and accrued expenses approximate the fair value because of their short maturities. We report our investment securities at their estimated fair value based on quoted market prices for identical or similar instruments.

Leases

We determine if an arrangement contains a lease at inception. We currently only have operating leases. We recognize a right-of-use operating lease asset and associated short- and long-term operating lease liability on our consolidated balance sheet for operating leases greater than one year. Our right-of-use assets represent our right to

use an underlying asset for the lease term and our lease liabilities represent our obligation to make lease payments arising from the lease arrangement. We recognize our right-of-use operating lease assets and lease liabilities based on the present value of the future minimum lease payments we will pay over the lease term. We determine the lease term at the inception of each lease, and in certain cases our lease term could include renewal options if we concluded we were reasonably certain that we will exercise the renewal option. When we exercise a lease option that was not previously included in the initial lease term, we reassess our right-of-use asset and lease liabilities for the new lease term.

As our current leases do not provide an interest rate implicit in the lease, we used our incremental borrowing rate, based on the information available on the date we adopted Topic 842 (January 2019), as of the lease inception date or at the lease option extension date in determining the present value of future payments. We recognize rent expense for our minimum lease payments on a straight-line basis over the expected term of our lease. We recognize period expenses, such as common area maintenance expenses, in the period we incur the expense.

Long-Lived Assets

We evaluate long-lived assets, which include property, plant and equipment and patent costs, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets. We recorded charges of \$1.9 million, \$2.2 million and \$0.8 million for the years ended December 31, 2020, 2019 and 2018, respectively, related to the write-down of patents.

Use of Estimates

The preparation of consolidated financial statements in conformity with accounting principles generally accepted in the U.S. requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Stock-Based Compensation Expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, RSUs, and stock purchase rights under our ESPP based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. On the grant date, we use our stock price and assumptions regarding a number of variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns.

We recognize compensation expense for option awards and RSUs using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), we recognize compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

The fair value of RSUs is based on the market price of our common stock on the date of grant. The RSUs we have granted vest annually over a four-year period. RSUs granted after June 2020 to our board of directors vest annually.

See Note 4, *Stockholders' Equity*, for additional information regarding our stock-based compensation plans.

Accumulated Other Comprehensive Loss

Accumulated other comprehensive loss is comprised of unrealized gains and losses on investments, net of taxes and currency translation adjustments. The following table summarizes changes in accumulated other comprehensive loss for the years ended December 31, 2020, 2019 and 2018 (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Beginning balance accumulated other comprehensive loss	\$(25,290)	\$(32,016)	\$(31,759)
Unrealized gains (losses) on securities, net of tax ⁽¹⁾	3,729	6,633	(280)
Currency translation adjustment	617	93	23
Adjustments to other comprehensive loss from purchase of noncontrolling interest of Akcea Therapeutics, Inc.	(127)	—	—
Net other comprehensive loss for the period	<u>4,219</u>	<u>6,726</u>	<u>(257)</u>
Ending balance accumulated other comprehensive loss	<u>\$(21,071)</u>	<u>\$(25,290)</u>	<u>\$(32,016)</u>

(1) We did not have tax expense included in our other comprehensive loss for the year ended December 31, 2020. For the years ended December 31, 2019 and 2018, we had a tax benefit \$1.4 million and \$0.3 million included in other comprehensive loss respectively.

Convertible Debt

At issuance, we accounted for our convertible debt instruments, including our 0.125 percent senior convertible notes, or 0.125% Notes, and 1 percent senior convertible notes, or 1% Notes, that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate on the date the notes were issued. In reviewing debt issuances, we were not able to identify any comparable companies that issued non-convertible debt instruments at the time of the issuance of the convertible notes. Therefore, we estimated the fair value of the liability component of our notes by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities.

We assigned a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording our debt at a discount. We are amortizing our debt issuance costs and debt discount over the life of the convertible notes as additional non-cash interest expense utilizing the effective interest method. For additional information, see Note 3, *Long-Term Obligations and Commitments*.

The 1% Notes mature in November 2021. Therefore, as of December 31, 2020, we classified the liability component of the 1% Notes as a current liability on our consolidated balance sheet.

In August 2020, the FASB issued guidance simplifying the accounting for convertible debt instruments. See the section titled “Impact of Recently Issued Accounting Standards” below for details.

Call Spread

In conjunction with the issuance of our 0.125% Notes, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants. We account for the note hedges and warrants as separate freestanding financial instruments and treat each instrument as a separate unit of accounting. We determined that the note hedges and warrants do not meet the definition of a liability using the guidance contained in ASC Topic 480, therefore we account for the note hedges and warrants using the Derivatives and Hedging – Contracts in Entity’s Own Equity accounting guidance contained in ASC Topic 815. We determined that the note hedges and warrants meet the definition of a derivative, are indexed to our stock and meet the criteria to be classified in shareholders’ equity. We recorded the aggregate amount paid for the note hedges and the aggregate amount received for the warrants as additional paid-in capital in our consolidated balance sheet. We reassess our ability to continue to classify the note hedges and warrants in shareholders’ equity at each reporting period.

Segment Information

Through 2020, we had two operating segments, our Ionis Core segment and Akcea Therapeutics. Akcea was focused on developing and commercializing medicines to treat patients with serious and rare diseases. We have provided segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviewed to assess operating performance and to make operating decisions through 2020. We allocated a portion of Ionis’ development, R&D support and general and administrative expenses to Akcea for work Ionis performed on behalf of Akcea and we billed Akcea for these expenses.

Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in equity securities in publicly held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. We classify most of our securities as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices.

The following tables present the major security types we held at December 31, 2020 and 2019 that we regularly measure and carry at fair value. At December 31, 2019, our ProQR investment was subject to trading restrictions until the fourth quarter of 2020, as a result we included a lack of marketability discount in valuing this investment, which is a Level 3 input. As of December 31, 2020, our ProQR investment was no longer subject to trading restrictions. As of December 31, 2020, we did not have any investments which we valued using Level 3 inputs. The following tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At December 31, 2020	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents ⁽¹⁾	\$ 221,125	\$221,125	\$ —
Corporate debt securities ⁽²⁾	846,315	—	846,315
Debt securities issued by U.S. government agencies ⁽⁴⁾	174,861	—	174,861
Debt securities issued by the U.S. Treasury ⁽³⁾	358,497	358,497	—
Debt securities issued by states of the U.S. and political subdivisions of the states ⁽⁴⁾	136,309	—	136,309
Other municipal debt securities ⁽⁴⁾	6,225	—	6,225
Investment in ProQR Therapeutics N.V. ⁽⁵⁾	2,031	2,031	—
Total	<u>\$1,745,363</u>	<u>\$581,653</u>	<u>\$1,163,710</u>

	At December 31, 2019	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents ⁽¹⁾	\$ 418,406	\$418,406	\$ —	\$ —
Corporate debt securities ⁽⁶⁾	1,102,568	—	1,102,568	—
Debt securities issued by U.S. government agencies ⁽⁷⁾	329,404	—	329,404	—
Debt securities issued by the U.S. Treasury ⁽⁴⁾	363,694	363,694	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states ⁽⁴⁾	40,407	—	40,407	—
Investment in ProQR Therapeutics N.V. ⁽⁵⁾	4,506	—	—	4,506
Total	<u>\$2,258,985</u>	<u>\$782,100</u>	<u>\$1,472,379</u>	<u>\$4,506</u>

(1) Included in cash and cash equivalents on our consolidated balance sheet.

(2) \$10.0 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(3) \$17.5 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(4) Included in short-term investments.

(5) Included in other current assets on our consolidated balance sheet.

(6) \$19.0 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(7) \$0.8 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

Income Taxes

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in our financial statements or tax returns. In addition, deferred tax assets are recorded for the future benefit of utilizing net operating losses and research and development credit carryforwards. We record a valuation allowance when necessary to reduce our net deferred tax assets to the amount expected to be realized.

We apply the authoritative accounting guidance prescribing a threshold and measurement attribute for the financial recognition and measurement of a tax position taken or expected to be taken in a tax return. We recognize liabilities for uncertain tax positions based on a two-step process. The first step is to evaluate the tax position for recognition by determining if the weight of available evidence indicates that it is more likely than not that the position will be sustained on audit, including resolution of related appeals or litigation processes, if any. The second step requires us to estimate and measure the tax benefit as the largest amount that is more than 50 percent likely to be realized upon ultimate settlement.

We are required to use significant judgment in evaluating our uncertain tax positions and determining our provision for income taxes. Although we believe our reserves are reasonable, no assurance can be given that the final tax outcome of these matters will not be different from that which is reflected in our historical income tax provisions and accruals. We adjust these reserves for changing facts and circumstances, such as the closing of a tax audit or the refinement of an estimate. To the extent that the final tax outcome of these matters is different than the amounts recorded, such differences may impact the provision for income taxes in the period in which such determination is made.

We are also required to use significant judgment in determining any valuation allowance recorded against our deferred tax assets. In assessing the need for a valuation allowance, we consider all available evidence, including scheduled reversal of deferred tax liabilities, past operating results, the feasibility of tax planning strategies and estimates of future taxable income. We base our estimates of future taxable income on assumptions that are consistent with our plans. The assumptions we use represent our best estimates and involve inherent uncertainties and the application of our judgment. Should actual amounts differ from our estimates, the amount of our tax expense and liabilities we recognize could be materially impacted. We record a valuation allowance to reduce the balance of our net deferred tax assets to the amount we believe is more-likely-than-not to be realized.

We do not provide for a U.S. income tax liability and foreign withholding taxes on undistributed foreign earnings of our foreign subsidiaries.

Impact of Recently Issued Accounting Standards

In June 2016, the FASB issued guidance that changes the measurement of credit losses for most financial assets and certain other instruments. If we have credit losses, this updated guidance requires us to record allowances for these instruments under a new expected credit loss model. This model requires us to estimate the expected credit loss of an instrument over its lifetime, which represents the portion of the amortized cost basis we do not expect to collect. The new guidance requires us to remeasure our allowance in each reporting period we have credit losses. We adopted this new guidance on January 1, 2020. This guidance did not have an impact on our consolidated financial statements.

In August 2018, the FASB issued clarifying guidance on how to account for implementation costs related to cloud-servicing arrangements. The guidance states that if these fees qualify to be capitalized and amortized over the service period, they need to be expensed in the same line item as the service expense and recognized in the same balance sheet category. The update can be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. We adopted this guidance on January 1, 2020 on a prospective basis. This guidance did not have an impact on our consolidated financial statements.

In November 2018, the FASB issued clarifying guidance of the interaction between the collaboration accounting guidance and the new revenue recognition guidance we adopted on January 1, 2018 (Topic 606). Below is the clarifying guidance and how we implemented it (in italics):

- 1) When a participant is considered a customer in a collaborative arrangement, all of the associated accounting under Topic 606 should be applied.
 - *We are applying all of the associated accounting under Topic 606 when we determine a participant in a collaborative arrangement is a customer.*

- 2) Adds “unit of account” concept to collaboration accounting guidance to align with Topic 606. The “unit of account” concept is used to determine if revenue is recognized or if a contra expense is recognized from consideration received under a collaboration.
 - *We use the “unit of account” concept when we receive consideration under a collaborative arrangement to determine when we recognize revenue or a contra expense.*
- 3) The clarifying guidance precludes us from recognizing revenue under Topic 606 when we determine a transaction with a collaborative partner is not a customer and is not directly related to the sales to third parties.
 - *When we conclude a collaboration partner is not a customer and is not directly related to the sales to third parties, we do not recognize revenue for the transaction.*

We adopted this new guidance on January 1, 2020. This guidance did not have any impact on our consolidated financial statements.

In August 2020, the FASB issued guidance which simplifies the accounting for convertible instruments, amends the guidance on derivative scope exceptions for contracts in an entity’s own equity, and modifies the guidance on diluted earnings per share calculations as a result of these changes. Under our current outstanding convertible debt arrangements, we anticipate the following impacts:

- 1) We will no longer separate our existing convertible debt into liability and equity components. Therefore, we will no longer recognize a debt discount for the value of the conversion option, instead we will record the face value of the convertible debt as a liability on our consolidated balance sheet;
- 2) We will record cash interest expense plus amortization of debt issuance costs to interest expense. Since we will not recognize a debt discount, we will no longer record the amortization of a debt discount to interest expense; and
- 3) We do not expect our EPS calculation to not change under this update. We plan to continue to use the if-converted method to calculate diluted earnings per share.

We plan to adopt this guidance in the first quarter of 2021 under the full retrospective approach, meaning we will apply the guidance to all periods presented beginning in the first quarter of 2021.

2. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2020:

One year or less	73%
After one year but within two years	18%
After two years but within three and a half years	<u>9%</u>
Total	<u>100%</u>

As illustrated above, at December 31, 2020, 91 percent of our available-for-sale securities had a maturity of less than two years.

All of our available-for-sale securities are available to us for use in our current operations. As a result, we categorize all of these securities as current assets even though the stated maturity of some individual securities may be one year or more beyond the balance sheet date.

At December 31, 2020, we had an ownership interest of less than 20 percent in seven private companies and two public companies with which we conduct business. The privately-held companies are Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd. The publicly traded companies are ATL and ProQR.

The following is a summary of our investments (in thousands):

December 31, 2020	Cost⁽¹⁾	Gross Unrealized		Estimated Fair Value
		Gains	Losses	
Available-for-sale securities:				
Corporate debt securities ⁽²⁾	\$ 514,182	\$ 2,194	\$ (41)	\$ 516,335
Debt securities issued by U.S. government agencies	94,234	354	(2)	94,586
Debt securities issued by the U.S. Treasury ⁽²⁾	307,576	233	(9)	307,800
Debt securities issued by states of the U.S. and political subdivisions of the states	104,271	196	(12)	104,455
Other municipal debt securities	5,191	—	(7)	5,184
Total securities with a maturity of one year or less	1,025,454	2,977	(71)	1,028,360
Corporate debt securities	325,079	4,941	(40)	329,980
Debt securities issued by U.S. government agencies	80,099	185	(9)	80,275
Debt securities issued by the U.S. Treasury	50,318	383	(4)	50,697
Debt securities issued by states of the U.S. and political subdivisions of the states	31,779	91	(16)	31,854
Other municipal debt securities	1,041	—	—	1,041
Total securities with a maturity of more than one year	488,316	5,600	(69)	493,847
Total available-for-sale securities	\$1,513,770	\$ 8,577	\$ (140)	\$1,522,207
Equity securities:				
Total equity securities included in other current assets ⁽³⁾	\$ 4,712	\$ —	\$ (2,681)	\$ 2,031
Total equity securities included in deposits and other assets ⁽⁴⁾	15,062	15,938	—	31,000
Total equity securities	\$ 19,774	\$15,938	\$ (2,681)	\$ 33,031
Total available-for-sale and equity securities	\$1,533,544	\$24,515	\$ (2,821)	\$1,555,238
December 31, 2019	Cost⁽¹⁾	Gross Unrealized		Estimated Fair Value
		Gains	Losses	
Available-for-sale securities:				
Corporate debt securities ⁽²⁾	\$ 669,665	\$1,451	\$ (43)	\$ 671,073
Debt securities issued by U.S. government agencies	188,216	303	(43)	188,476
Debt securities issued by the U.S. Treasury ⁽²⁾	327,670	232	(27)	327,875
Debt securities issued by states of the U.S. and political subdivisions of the states	21,065	26	(5)	21,086
Total securities with a maturity of one year or less	1,206,616	2,012	(118)	1,208,510
Corporate debt securities	428,627	2,911	(43)	431,495
Debt securities issued by U.S. government agencies	140,988	57	(117)	140,928
Debt securities issued by the U.S. Treasury	35,822	9	(12)	35,819
Debt securities issued by states of the U.S. and political subdivisions of the states	19,309	18	(6)	19,321
Total securities with a maturity of more than one year	624,746	2,995	(178)	627,563
Total available-for-sale securities	\$1,831,362	\$5,007	\$ (296)	\$1,836,073
Equity securities:				
Total equity securities included in other current assets ⁽³⁾	\$ 4,712	\$ —	\$ (870)	\$ 3,842
Total equity securities included in deposits and other assets ⁽⁴⁾	10,000	—	—	10,000
Total equity securities	\$ 14,712	\$ —	\$ (870)	\$ 13,842
Total available-for-sale and equity securities	\$1,846,074	\$5,007	\$ (1,166)	\$1,849,915

(1) We hold our available-for-sale securities at amortized cost.

(2) Includes investments classified as cash equivalents on our consolidated balance sheet.

(3) Our equity securities included in other current assets consisted of our investments in publicly traded companies. We recognize publicly traded equity securities at fair value.

(4) Our equity securities included in deposits and other assets consisted of our investments in privately held companies. We recognize our private company equity securities at cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer on our consolidated balance sheet.

The following is a summary of our investments we considered to be temporarily impaired at December 31, 2020 (in thousands). All of these investments have less than 12 months of temporary impairment. We believe that the decline in value of these securities is temporary and is primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold our debt securities to maturity. Therefore, we anticipate full recovery of our debt securities' amortized cost basis at maturity.

	<u>Number of Investments</u>	<u>Estimated Fair Value</u>	<u>Unrealized Losses</u>
Corporate debt securities	54	\$121,162	\$ (81)
Debt securities issued by U.S. government agencies	2	29,988	(11)
Debt securities issued by the U.S. Treasury	8	76,941	(13)
Debt securities issued by states of the U.S. and political subdivisions of the states	160	49,832	(28)
Other municipal debt securities	<u>2</u>	<u>6,225</u>	<u>(7)</u>
Total temporarily impaired securities	<u>226</u>	<u>\$284,148</u>	<u>\$(140)</u>

3. Long-Term Obligations and Commitments

The carrying value of our long-term obligations was as follows (in thousands):

	<u>December 31,</u>	
	<u>2020</u>	<u>2019</u>
0.125 percent convertible senior notes	\$ 455,719	\$434,711
1 percent convertible senior notes ⁽¹⁾	293,161	275,333
Long-term mortgage debt	59,984	59,913
Leases and other obligations	<u>30,710</u>	<u>17,569</u>
Total	\$ 839,574	\$787,526
Less: current portion ⁽¹⁾	<u>(300,462)</u>	<u>(2,026)</u>
Total Long-Term Obligations	<u>\$ 539,112</u>	<u>\$785,500</u>

(1) We classified the carrying value of our 1% Notes as a current liability on our consolidated balance sheet at December 31, 2020 because it matures in November 2021.

Convertible Notes and Call Spread

0.125 Percent Convertible Senior Notes

In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange \$375.6 million of our 1% Notes for \$439.3 million of our 0.125% Notes, and to issue \$109.5 million of our 0.125% Notes. We completed this exchange to reduce our cash interest payments, increase our conversion price and extend our maturity for a large portion of our debt. Additionally, in conjunction with the December 2019 exchange, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the effective conversion price even further.

Interest is payable semi-annually on June 15 and December 15 of each year for the 0.125% Notes. The 0.125% Notes are convertible at the option of the note holders prior to August 1, 2024 only under certain conditions. On or after August 1, 2024, the 0.125% Notes are initially convertible into approximately 6.6 million shares of common stock at a conversion price of approximately \$83.28 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the 0.125% Notes prior to maturity, and no sinking fund is provided for them. If we undergo a fundamental change, holders may require us to purchase for cash all or any portion of their 0.125% Notes at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest to, but excluding, the fundamental change purchase date.

At December 31, 2020, we had the following 0.125% Notes outstanding (amounts in millions except price per share data):

	<u>0.125% Notes</u>
Outstanding principal balance	\$548.8
Maturity date	December 15, 2024
Interest rate	0.125%
Conversion price per share	\$83.28
Total shares of common stock subject to conversion	6.6

The following table summarizes information about the equity and liability components of our outstanding 0.125% Notes (in millions). We measured the fair values of the convertible notes outstanding based on quoted market prices, which is a Level 2 measurement at December 31, 2020 and 2019:

	<u>December 31,</u>	
	<u>2020</u>	<u>2019</u>
Fair value of outstanding notes	\$564.9	\$558.7
Principal amount of convertible notes outstanding	\$548.8	\$548.8
Unamortized portion of debt discount	\$ 86.0	\$105.2
Long-term debt	\$455.7	\$434.7
Carrying value of equity component	\$105.8	\$105.8

Call Spread

Additionally, in conjunction with the December 2019 exchange, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the conversion price even further. The call spread cost us \$52.6 million, of which \$108.7 million was for the note hedge purchase, offset by \$56.1 million we received for selling the warrants. We increased our effective conversion price to \$123.38 with the same number of underlying shares as our 0.125% Notes. We accounted for our call spread transactions using the Derivatives and Hedging – Contracts in Entity’s Own Equity accounting guidance contained in Topic 815. We determined that the call spread transactions meet the definition of a derivative, are indexed to our stock and meet the criteria to be classified in shareholders’ equity.

Similar to our 0.125% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0.125% Notes. The note hedges will expire upon maturity of 0.125% Notes, or December 2024. The note hedges and warrants are separate transactions and are not part of the terms of our 0.125% Notes. The holders of the 0.125% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the aggregate amount paid for the note hedges and the aggregate amount received for the warrants in additional paid-in capital in our consolidated balance sheet. We reassess our ability to continue to classify the note hedges and warrants in shareholders’ equity at each reporting period. We excluded shares under the note hedges from our calculation of diluted earnings per share as they were antidilutive. We will include the shares issuable under the warrants in our calculation of diluted earnings per share when the average market price per share of our common stock for the reporting period exceeds the strike price of the warrants.

1 Percent Convertible Senior Notes

In November 2014, we completed a \$500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1% Notes to repurchase \$140 million in principal of our 2¾ percent convertible senior notes, or 2¾% Notes. In December 2016, we issued an additional \$185.5 million of 1% Notes in exchange for the redemption of \$61.1 million of our 2¾% Notes. In December 2019, we exchanged a portion of our 1% Notes for 0.125% Notes. As a result, the principal balance of 1% Notes was \$309.9 million. Additionally, we recorded a \$21.9 million non-cash loss on early retirement of debt, reflecting the early retirement of a significant portion of our 1% Notes in December 2019.

At December 31, 2020, we had the following 1% Notes outstanding (amounts in millions except price per share data):

	<u>1% Notes</u>
Outstanding principal balance	\$309.9
Maturity date	November 30, 2021
Interest rate	1 percent
Conversion price per share	\$66.81
Total shares of common stock subject to conversion	4.6

Interest is payable semi-annually in arrears on May 15 and November 15 of each year for the 1% Notes. The 1% Notes are convertible at the option of the note holders prior to July 1, 2021 only under certain conditions. On or after July 1, 2021, the 1% Notes are initially convertible into approximately 4.6 million shares of common stock at a conversion price of approximately \$66.81 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the 1% Notes prior to maturity, and no sinking fund is provided for them. If we undergo a fundamental change, holders may require us to purchase for cash all or any portion of their 1% Notes at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest to, but excluding, the fundamental change purchase date.

The following table summarizes information about the equity and liability components of our outstanding 1% Notes (in millions). We measured the fair values of the convertible notes outstanding based on quoted market prices, which is a Level 2 measurement at December 31, 2020 and 2019:

	<u>December 31,</u>	
	<u>2020</u>	<u>2019</u>
Fair value of outstanding notes	\$338.5	\$354.8
Principal amount of convertible notes outstanding	\$309.9	\$309.9
Unamortized portion of debt discount	\$ 15.8	\$ 32.8
Current/long-term debt	\$293.2	\$275.3
Carrying value of equity component	\$ 33.5	\$ 33.5

We account for our convertible notes using an accounting standard that requires us to assign a value to our convertible debt equal to the estimated fair value of similar debt instruments without the conversion feature and to record the remaining portion in equity. As a result, we recorded our convertible notes at a discount, which we are amortizing as additional non-cash interest expense over the expected life of the respective debt. We determined our nonconvertible debt borrowing rate using a combination of the present value of the debt's cash flows and a Black-Scholes valuation model. The following table summarizes the nonconvertible borrowing rate, effective interest rate and amortization period of our debt discount for our convertible notes:

	<u>1% Notes</u>	<u>0.125% Notes</u>
Nonconvertible debt borrowing rate	7.4 percent	4.4 percent
Effective interest rate ⁽¹⁾	7.5 percent	4.9 percent
Amortization period of debt discount	7 years	5 years

(1) For our 1% Notes, our effective interest rate represents our effective interest rate after our December 2019 debt exchange.

Our total interest expense for our outstanding senior convertible notes for the years ended December 31, 2020, 2019 and 2018 included \$38.7 million, \$39.3 million and \$35.2 million, respectively, of non-cash interest expense related to the amortization of the debt discount and debt issuance costs for our convertible notes.

Financing Arrangements

Line of Credit Arrangement

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley, which we amended in February 2016. Under the amended credit agreement, Morgan Stanley provided a maximum of \$30 million of revolving credit for general working capital purposes. During the third quarter of 2019, we paid off our total outstanding borrowings of \$12.5 million under the agreement and subsequently terminated the agreement.

Research and Development and Manufacturing Facilities

In July 2017, we purchased the building that houses our primary R&D facility for \$79.4 million and our manufacturing facility for \$14.0 million. We financed the purchase of these two facilities with mortgage debt of \$60.4 million in total. Our primary R&D facility mortgage has an interest rate of 3.88 percent. Our manufacturing facility mortgage has an interest rate of 4.20 percent. During the first five years of both mortgages, we are only required to make interest payments. Both mortgages mature in August 2027.

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2020 are as follows (in thousands):

2021.....	\$ 329,189
2022.....	3,495
2023.....	4,180
2024.....	553,006
2025.....	3,494
Thereafter	<u>60,933</u>
Subtotal	\$ 954,297
Less: current portion.....	(300,462)
Less: fixed and determinable interest	(21,758)
Less: unamortized portion of debt discount	(101,820)
Less: debt issuance costs	(8,455)
Plus: lease liabilities.....	<u>17,310</u>
Total long-term debt.....	<u>\$ 539,112</u>

Operating Leases

Carlsbad Leases

We lease a facility adjacent to our manufacturing facility that has laboratory and office space that we use to support our manufacturing facility. We lease this space under a non-cancelable operating lease. In May 2020, we exercised our option to extend our lease, extending our lease term from June 2021 to August 2026. We have one remaining option to extend the lease for an additional five-year period.

We also lease additional office spaces in Carlsbad. We lease these spaces under non-cancelable operating leases with initial terms ending in 2023 with options to extend each of the leases for one five-year period.

Boston Lease

We entered into an operating lease agreement for office space located in Boston, Massachusetts in the second quarter of 2018. The lease commencement date was in August 2018 and we took occupancy in September 2018. We are leasing this space under a non-cancelable operating lease with an initial term ending after 123 months and an option to extend the lease for an additional five-year term. Under the lease agreement, we received a three-month free rent period, which commenced on August 15, 2018, and a tenant improvement allowance up to \$3.8 million. We provided the lessor with a letter of credit to secure its obligations under the lease in the initial amount of \$2.4 million, to be reduced to \$1.8 million on the third anniversary of the rent commencement date and to \$1.2 million on the fifth anniversary of the rent commencement date if we meet certain conditions set forth in the lease at each such time.

When we determined our lease term for our operating lease right-of-use assets and lease liabilities for these leases, we did not include the extension options for these leases in the original lease term.

Amounts related to our operating leases were as follows (dollar amounts in millions):

	<u>At December 31, 2020</u>
Right-of-use operating lease assets ⁽¹⁾	\$13.1
Operating lease liabilities ⁽²⁾	\$17.3
Weighted average remaining lease term	7.2 years
Weighted average discount rate	7.0%

(1) Included in deposits and other assets on our consolidated balance sheet.

(2) Current portion of \$2.0 million was included in current portion of long-term obligations on our consolidated balance sheet, with the difference included in long-term obligations.

During the years ended December 31, 2020, 2019, and 2018 we paid \$3.8 million, \$3.9 million and \$1.7 million of lease payments, which were included in operating activities in our consolidated statement of cash flows.

As of December 31, 2020, the future payments for our operating lease liabilities are as follows (in thousands):

	<u>Operating Leases</u>
Year ending December 31,	
2021	\$ 3,193
2022	2,968
2023	2,707
2024	2,583
2025	2,442
Thereafter	<u>7,038</u>
Total minimum lease payments	20,931
Less:	
Imputed interest	<u>(3,621)</u>
Total operating lease liabilities	<u>\$17,310</u>

Rent expense was \$3.7 million, \$3.6 million and \$2.6 million for the years ended December 31, 2020, 2019 and 2018, respectively.

4. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15 million shares of "blank check" Preferred Stock. As of December 31, 2020, there were no shares of Preferred Stock outstanding. We have designated Series C Junior Participating Preferred Stock but have no issued or outstanding shares as of December 31, 2020.

Common Stock

At December 31, 2020 and 2019, we had 300 million shares of common stock authorized, of which 140.4 million and 140.3 million were issued and outstanding, respectively. As of December 31, 2020, total common shares reserved for future issuance were 26.1 million.

During the years ended December 31, 2020, 2019 and 2018, we issued 1.7 million, 3.1 million and 1.5 million shares of common stock, respectively, for stock option exercises, vesting of restricted stock units, and ESPP purchases. We received net proceeds from these transactions of \$52.0 million, \$119.7 million and \$27.9 million in 2020, 2019 and 2018, respectively.

Share Repurchase Program

In September 2019, our board of directors approved a share repurchase program of up to \$125 million of our common stock. In 2019, we repurchased 535,000 shares for \$34.4 million. In the first quarter of 2020, we repurchased an additional 1.5 million shares for \$90.5 million.

Stock Plans

1989 Stock Option Plan

In June 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20.0 million shares of common stock to our employees, directors, and consultants. The plan expires in January 2024. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. At December 31, 2020, a total of 30 thousand options were outstanding, of which options to purchase 30 thousand shares were exercisable, and 50 thousand shares were available for future grant under the 1989 Plan.

2011 Equity Incentive Plan

In March 2011, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, and performance cash awards to our employees, directors, and consultants. In June 2015, May 2017 and June 2019, after receiving approval from our stockholders, we amended our 2011 Equity Incentive Plan to increase the total number of shares reserved for issuance. We increased the shares available under our 2011 Equity Incentive Plan from 5.5 million to 11.0 million in June 2015, from 11.0 million to 16.0 million in May 2017 and from 16.0 million to 23.0 million in June 2019. The plan expires in June 2031. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only options and restricted stock unit awards to our employees, directors and consultants. We have granted restricted stock unit awards to our employees under the 2011 Plan which vest annually over a four-year period. At December 31, 2020, a total of 11.4 million options were outstanding, of which 6.7 million were exercisable, 2.2 million restricted stock unit awards were outstanding, and 4.3 million shares were available for future grant under the 2011 Plan.

Under the 2011 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur. The stock options and restricted stock unit awards we issued to Dr. Stanley T. Crooke in his former role as chief executive officer and certain stock options and restricted stock unit awards we issued to B. Lynne Parshall in her former role as chief operating officer will accelerate upon a change of control, as defined in the 2011 Plan. In addition, we implemented a change of control and severance benefit plan that provides for change of control and severance benefits to our executive officers, including our chief executive officer and chief financial officer. If we terminate one of our executive officers or if an executive officer resigns for good reason during the period that begins three months before and ends twelve months following a change in control of the company, the impacted executive officers' stock options and RSUs vesting will accelerate for options and RSUs outstanding as of the termination date.

2020 Equity Incentive Plan

In connection with the Akcea Acquisition in October 2020, we assumed the unallocated portion of the available share reserve under the Akcea 2015 Equity Incentive Plan. In December 2020, we amended and restated the Akcea 2015 equity plan, including renaming the plan as the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, or 2020 Plan. The 2020 Plan provided for the issuance of up to 2.6 million shares of our Common Stock to our employees, directors and consultants who were employees of Akcea prior to the Akcea Acquisition.

The plan expires in December 2025. The 2020 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation

rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only options and restricted stock unit awards to our eligible employees, directors and consultants. We have granted stock options to our employees under the 2020 Plan which vest annually over a four-year period. At December 31, 2020, a total of 0.01 million options were outstanding, of which none were exercisable, and 2.6 million shares were available for future grant under the 2020 Plan.

Under the 2020 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur.

Corporate Transactions and Change in Control under 2011 and 2020 Plans

In the event of certain significant corporate transactions, our Board of Directors has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 and 2020 Plans:

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and
- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options and restricted stock units to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan, or the 2002 Plan. In June 2015, after receiving approval from our stockholders, we amended our 2002 Plan to increase the total number of shares reserved for issuance from 1.2 million to 2.0 million. In June 2020, after receiving approval from our stockholders, we further amended our 2002 Plan. The amendments included:

- An increase to the total number of shares reserved for issuance under the plan from 2.0 million to 2.8 million shares;
- A reduction to the amount of the automatic awards under the plan;
- A revision to the vesting schedule of new awards granted; and
- An extension of the term of the plan.

Options under this plan expire 10 years from the date of grant. At December 31, 2020, a total of 1.0 million options were outstanding, of which 0.6 million were exercisable, 0.1 million restricted stock unit awards were outstanding, and 0.8 million shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In June 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years until 2019, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 3.2 million shares authorized under the plan as of December 31, 2020. The ESPP permits

full-time employees to purchase common stock through payroll deductions (which cannot exceed 10 percent of each employee's compensation) at the lower of 85 percent of fair market value at the beginning of the purchase period or the end of each purchase period. Under the amended and restated ESPP, employees must hold the stock they purchase for a minimum of six months from the date of purchase. During 2020, employees purchased and we issued to employees 0.06 million shares under the ESPP at a weighted average price of \$43.65 per share. At December 31, 2020, there were 0.7 million shares available for purchase under the ESPP.

Stock Option Activity

The following table summarizes the stock option activity under our stock plans for the year ended December 31, 2020 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Exercise Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2019	11,001	\$51.48		
Granted	2,764	\$59.89		
Exercised	(1,069)	\$40.88		
Cancelled/forfeited/expired	<u>(361)</u>	\$56.48		
Outstanding at December 31, 2020	<u>12,335</u>	\$54.14	4.16	\$55,885
Exercisable at December 31, 2020	<u>7,366</u>	\$52.45	3.16	\$43,267

The weighted-average estimated fair values of options granted were \$29.43, \$28.76 and \$25.49 for the years ended December 31, 2020, 2019 and 2018, respectively. The total intrinsic value of options exercised during the years ended December 31, 2020, 2019 and 2018 were \$15.5 million, \$83.8 million and \$34.8 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was \$43.7 million, \$105.9 million and \$18.9 million for the years ended December 31, 2020, 2019 and 2018, respectively. For the year ended December 31, 2020, the weighted-average fair value of options exercised was \$55.33. As of December 31, 2020, total unrecognized compensation cost related to non-vested stock options was \$54.1 million. We expect to recognize this cost over a weighted average period of 1.1 years. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures.

Restricted Stock Unit Activity

The following table summarizes the RSU activity for the year ended December 31, 2020 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2019	1,866	\$55.80
Granted	1,244	\$60.86
Vested	(602)	\$53.68
Cancelled/forfeited	<u>(134)</u>	\$58.96
Non-vested at December 31, 2020	<u>2,374</u>	\$58.81

For the years ended December 31, 2020, 2019 and 2018, the weighted-average grant date fair value of RSUs granted was \$60.86, \$60.23 and \$51.06 per RSU, respectively. As of December 31, 2020, total unrecognized compensation cost related to RSUs was \$55.3 million. We expect to recognize this cost over a weighted average period of 1.3 years. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures.

Stock-based Compensation Expense and Valuation Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2020, 2019 and 2018 (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Cost of products sold	\$ 1,991	\$ 438	\$ 160
Research, development and patent	115,584	95,348	76,557
Selling, general and administrative	112,542	50,788	54,595
Total	<u>\$230,117</u>	<u>\$146,574</u>	<u>\$131,312</u>

Our non-cash stock-based compensation expense included \$94.8 million, \$37.1 million and \$44.3 million of stock-based compensation expense for Akcea employees for the years ended December 31, 2020, 2019 and 2018, respectively.

In October 2020, as part of the Akcea Acquisition, Akcea's outstanding equity awards vested under Akcea's Plan. As a result, in the fourth quarter of 2020, we recognized all unrecognized stock-based compensation (\$59.3 million) under Akcea's Plan. See Note 7, *Akcea Acquisition*, in the Notes to the Consolidated Financial Statements for further details.

In the third quarter of 2019, three Akcea executive officers terminated their employment and entered into separation agreements with Akcea. As a result, in the third quarter of 2019, Akcea reversed \$19.1 million of stock-based compensation expense it had previously recognized related to the executive officers' stock options and RSUs that were no longer going to vest.

Determining Fair Value

Valuation. We measure stock-based compensation expense for equity-classified awards, principally related to stock options, RSUs, and stock purchase rights under the ESPP at the grant date, based on the estimated fair value of the award and we recognize the expense over the employee's requisite service period. We value RSUs based on the market price of our common stock on the date of grant.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on actual and projected exercise patterns. We recognize compensation expense for stock options granted, RSUs, and stock purchase rights under the ESPP using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), we recognize compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

For the years ended December 31, 2020, 2019 and 2018, we used the following weighted-average assumptions in our Black-Scholes calculations:

Ionis Employee Stock Options:

	December 31,		
	2020	2019	2018
Risk-free interest rate	1.5%	2.3%	2.4%
Dividend yield	0.0%	0.0%	0.0%
Volatility	58.6%	60.3%	63.0%
Expected life	4.7 years	4.8 years	4.6 years

Ionis Board of Director Stock Options:

	December 31,		
	2020	2019	2018
Risk-free interest rate	0.5%	1.9%	2.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	57.6%	60.7%	61.5%
Expected life	6.7 years	6.6 years	6.6 years

Ionis ESPP:

	December 31,		
	2020	2019	2018
Risk-free interest rate	0.8%	2.4%	1.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	47.9%	45.6%	47.3%
Expected life	6 months	6 months	6 months

Risk-Free Interest Rate. We base the risk-free interest rate assumption on observed interest rates appropriate for the term of our stock option plans or ESPP.

Dividend Yield. We base the dividend yield assumption on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future.

Volatility. We use an average of the historical stock price volatility of our stock for the Black-Scholes model. We computed the historical stock volatility based on the expected term of the awards.

Expected Life. The expected term of stock options we have granted represents the period of time that we expect them to be outstanding. We estimated the expected term of options we have granted based on actual and projected exercise patterns.

Forfeitures. We reduce stock-based compensation expense for estimated forfeitures. We estimate forfeitures at the time of grant and revise, if necessary, in subsequent periods if actual forfeitures differ from those estimates. We estimate forfeitures based on historical experience.

In addition to our stock plans, Akcea had its own stock plan prior to the Akcea Acquisition, referred to as the Akcea 2015 Equity Incentive Plan, or Akcea Plan. Under the Akcea Plan, Akcea granted options and RSUs.

For the years ended December 31, 2020, 2019 and 2018, we used the following weighted-average assumptions in our Black-Scholes calculations for the Akcea Plan:

Akcea Employee Stock Options:

	December 31,		
	2020	2019	2018
Risk-free interest rate	1.1%	2.2%	2.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	75.0%	75.4%	77.1%
Expected life	6.08 years	6.09 years	6.08 years

Akcea Board of Director Stock Options:

	December 31,		
	2020	2019	2018
Risk-free interest rate	0.8%	1.8%	2.9%
Dividend yield	0.0%	0.0%	0.0%
Volatility	75.3%	73.8%	78.2%
Expected life	5.67 years	6.25 years	6.42 years

Akcea ESPP:

	<u>December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
Risk-free interest rate	1.0%	2.4%	1.9%
Dividend yield	0.0%	0.0%	0.0%
Volatility	71.9%	60.0%	64.2%
Expected life	6 months	6 months	6 months

The following summarizes the Black-Scholes input methodology for Akcea options that differs from the methodology we use for Ionis options:

Volatility. Since Akcea did not have sufficient history to estimate the volatility of its common stock, Akcea calculated its expected volatility based on a blend of its historical volatility and reported data from selected publicly traded peer companies for which historical information was available.

Expected Life. Since Akcea did not have sufficient historical information, it used the simplified method for estimating its expected term. Under the simplified method Akcea calculated its expected term as the average time-to-vesting and the contractual life of the options.

Akcea RSU's

The fair value of RSUs was based on the market price of Akcea's common stock on the date of grant. Akcea granted RSUs with various vesting terms between six months and four years. The weighted-average grant date fair value of RSUs granted to employees for years ended December 31, 2020 and 2019 was \$15.57 and \$21.95 per share, respectively.

5. Income Taxes

Income (loss) before income taxes is comprised of (in thousands):

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
United States	\$(172,702)	\$344,280	\$(69,576)
Foreign	<u>2,670</u>	<u>2,489</u>	<u>(6,580)</u>
Income (loss) before income taxes	<u><u>\$(170,032)</u></u>	<u><u>\$346,769</u></u>	<u><u>\$(76,156)</u></u>

Our income tax expense (benefit) was as follows (in thousands):

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
Current:			
Federal	\$ (837)	\$35,861	\$ 438
State	3,782	14,329	(1,442)
Foreign	<u>518</u>	<u>413</u>	<u>374</u>
Total current income tax expense (benefit)	3,463	50,603	(630)
Deferred:			
Federal	313,271	(7,096)	(290,511)
State	<u>—</u>	<u>—</u>	<u>—</u>
Total deferred income tax benefit	<u>313,271</u>	<u>(7,096)</u>	<u>(290,511)</u>
Total income tax expense (benefit)	<u><u>\$316,734</u></u>	<u><u>\$43,507</u></u>	<u><u>\$(291,141)</u></u>

Our expense (benefit) for income taxes differs from the amount computed by applying the U.S. federal statutory rate to income (loss) before taxes. The sources and tax effects of the differences are as follows (in thousands):

	Year Ended December 31,					
	2020		2019		2018	
Pre-tax income (loss)	\$(170,032)		\$346,769		\$ (76,156)	
Statutory rate	(35,707)	21.0%	72,822	21.0%	(15,993)	21.0%
State income tax net of federal benefit	(39,230)	23.1%	49,119	14.2%	(2,202)	2.9%
Foreign	49	0.0%	340	0.1%	1,735	(2.3)%
Net change in valuation allowance	437,597	(257.4)%	(37,765)	(10.9)%	(277,924)	364.9%
Net operating loss expiration	—	0.0%	—	0.0%	8,864	(11.6)%
TEGSEDI licensing gain	—	0.0%	—	0.0%	59,583	(78.2)%
Impact from outside basis differences	—	0.0%	(16,344)	(4.7)%	—	0.0%
Tax credits	(18,774)	11.0%	(22,296)	(6.4)%	(73,362)	96.3%
Deferred tax true-up	(206)	0.1%	646	0.2%	9,947	(13.1)%
Tax rate change	(29,131)	17.1%	1,811	0.5%	(1,808)	2.4%
Non-deductible compensation	7,931	(4.7)%	3,361	1.0%	3,154	(4.1)%
Other non-deductible items	193	(0.1)%	329	0.1%	(569)	0.7%
Stock-based compensation	17,435	(10.3)%	(4,837)	(1.4)%	(4,199)	5.5%
Foreign-derived intangible income benefit	—	0.0%	(2,071)	(0.6)%	—	0.0%
Impacts from Akcea Acquisition	(22,032)	13.0%	—	—	—	—
Other	(1,391)	0.8%	(1,608)	(0.5)%	1,633	(2.1)%
Effective rate	<u>\$ 316,734</u>	<u>(186.4)%</u>	<u>\$ 43,507</u>	<u>12.6%</u>	<u>\$(291,141)</u>	<u>382.3%</u>

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes.

Significant components of our deferred tax assets and liabilities as of December 31, 2020 and 2019 are as follows (in thousands):

	Year Ended December 31,	
	2020	2019
Deferred Tax Assets:		
Net operating loss carryovers	\$ 83,681	\$ 20,191
Tax credits	245,746	210,455
Deferred revenue	124,452	127,763
Stock-based compensation	80,055	65,703
Intangible and capital assets	98,443	77,861
Other	<u>13,402</u>	<u>12,510</u>
Total deferred tax assets	\$ 645,779	\$ 514,483
Deferred Tax Liabilities:		
Convertible debt	\$ (2,920)	\$ (6,110)
Fixed assets	(3,611)	(1,958)
Other	<u>(5,808)</u>	<u>(3,884)</u>
Net deferred tax asset	\$ 633,440	\$ 502,531
Valuation allowance	<u>(633,440)</u>	<u>(196,974)</u>
Total net deferred tax assets and liabilities	<u>\$ —</u>	<u>\$ 305,557</u>

We evaluate our deferred tax assets regularly to determine whether adjustments to the valuation allowance are appropriate due to changes in facts or circumstances, such as changes in expected future pre-tax earnings, tax law, interactions with taxing authorities and developments in case law. In making this evaluation, we rely on our recent history of pre-tax earnings. Our material assumptions are our forecasts of future pre-tax earnings and the nature and timing of future deductions and income represented by the deferred tax assets and liabilities, all of which involve the exercise of significant judgment. Although we believe our estimates are reasonable, we are required to use significant judgment in determining the appropriate amount of valuation allowance recorded against our deferred tax assets.

Ionis and Akcea have filed separate U.S. federal income tax returns since Akcea's IPO in 2017. Accordingly, we were required to assess our Ionis stand-alone and Akcea's valuation allowances separately even though we consolidate Akcea's financial results in our consolidated financial statements. However, as a result of the Akcea acquisition, Ionis and Akcea will file a consolidated U.S. federal income tax return beginning in the fourth quarter of 2020, and we therefore assessed our U.S. federal valuation allowance requirements on a consolidated basis as of that period. We continue to assess the state portion of our valuation allowance on a consolidated basis.

We assessed our valuation allowance requirements and recorded a valuation allowance of \$313 million against all of Ionis' U.S. federal net deferred tax assets in the fourth quarter of 2020, due to uncertainties related to our ability to realize the tax benefits associated with these assets. This determination is based largely on Akcea rejoining the Ionis U.S. consolidated federal tax group in the fourth quarter of 2020. Due to Akcea's historical and projected financial statement losses, and the negative impact this is expected to have on Ionis' consolidated taxable income, there is uncertainty of generating sufficient consolidated pre-tax income in future periods to realize the Ionis deferred tax benefits. It is also expected that Ionis' pre-tax income in future periods may be lower due to increased research and development expenses associated with our pipeline of wholly owned medicines. We now maintain a valuation allowance against all our consolidated U.S. federal and state net deferred tax assets.

Our valuation allowance increased by \$436 million from December 31, 2019 to December 31, 2020. \$313 million of the increase related to the valuation allowance established against our beginning of the year balance of Ionis' U.S. federal net deferred tax assets as discussed above, which resulted in us recognizing income tax expense during 2020. The remaining increase in our valuation allowance related to current year changes in our net deferred tax assets.

At December 31, 2020, we had federal and state, primarily California, tax net operating loss carryforwards of \$243.3 million and \$346.3 million, respectively. Our federal tax loss carryforwards are available indefinitely. Our California tax loss carryforwards will begin to expire in 2031. At December 31, 2020, we also had federal and California research and development tax credit carryforwards of \$210.5 million and \$87.4 million, respectively. Our Federal research and development tax credit carryforwards will begin to expire in 2034. Our California research and development tax credit carryforwards are available indefinitely.

Utilization of the net operating loss and tax credit carryforwards may be subject to an annual limitation due to the ownership change limitations provided by the Internal Revenue Code of 1986, as amended, and similar state provisions. The annual limitation may result in the expiration of net operating losses and credits before utilization.

We analyze filing positions in all U.S. federal, state and foreign jurisdictions where we file income tax returns, and all open tax years in these jurisdictions to determine if we have any uncertain tax positions on any of our income tax returns. We recognize the impact of an uncertain tax position on an income tax return at the largest amount that the relevant taxing authority is more-likely-than not to sustain upon audit. We do not recognize uncertain income tax positions if they have less than 50 percent likelihood of the applicable tax authority sustaining our position.

The following table summarizes our gross unrecognized tax benefits (in thousands):

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
Beginning balance of unrecognized tax benefits	\$ 69,784	\$68,301	\$ 78,014
Decrease for prior period tax positions	(24,154)	(867)	(12,814)
Increase for prior period tax positions	7,023	736	—
Increase for current period tax positions	<u>1,510</u>	<u>1,614</u>	<u>3,101</u>
Ending balance of unrecognized tax benefits	<u>\$ 54,163</u>	<u>\$69,784</u>	<u>\$ 68,301</u>

Included in the balance of unrecognized tax benefits at December 31, 2020 and 2019 was \$6.4 million and \$0.4 million respectively, that if we recognized, could impact our effective tax rate, subject to our remaining valuation allowance. None of our unrecognized tax benefits recorded at December 31, 2018 would impact our effective tax rate, if we recognized them.

We do not foresee any material changes to our gross unrecognized tax benefits within the next twelve months.

We recognize interest and/or penalties related to income tax matters in income tax expense. During the year ended December 31, 2020, we recognized \$0.3 million of accrued interest and penalties related to gross unrecognized tax benefits. We did not record any accrued interest and penalties for the years ended December 31, 2019 and 2018.

We are subject to taxation in the U.S. and various state and foreign jurisdictions. Our tax years for 1999 through 2019 are subject to examination by the U.S. federal, state and foreign tax authorities.

We do not provide for a U.S. income tax liability and foreign withholding taxes on undistributed foreign earnings of our foreign subsidiaries as we consider those earnings to be permanently reinvested. It is not practicable for us to calculate the amount of unrecognized deferred tax liabilities associated with these earnings.

6. Collaborative Arrangements and Licensing Agreements

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. We and Biogen are currently developing eight investigational medicines to treat neurodegenerative diseases under these collaborations, including medicines in development to treat people with ALS, Alzheimer's disease and Parkinson's disease. In addition to these medicines, our collaborations with Biogen include a substantial research pipeline that addresses a broad range of neurological diseases. From inception through December 2020, we have received more than \$2.8 billion from our Biogen collaborations.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. SPINRAZA is approved in over 50 countries around the world. From inception through December 2020, we earned more than \$1.3 billion in total revenue under our SPINRAZA collaboration, including more than \$930 million in revenue from SPINRAZA royalties and more than \$435 million in R&D revenue. We are receiving tiered royalties ranging from 11 percent to 15 percent on net sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on net sales of SPINRAZA. Biogen is responsible for all global development, regulatory and commercialization activities and costs for SPINRAZA. We completed our performance obligations under our collaboration in 2016.

New antisense medicines for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen has the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for global development, regulatory and commercialization activities and costs for such therapies. Under the collaboration agreement, we received a \$25 million upfront payment in the fourth quarter of 2017. We will receive development and regulatory milestone payments from Biogen if new medicines advance towards marketing approval. In total over the term of our collaboration, we are eligible to receive up to \$1.2 billion in license fees, milestone payments and other payments, including up to \$80 million for the achievement of development milestones, up to \$180 million for the achievement of commercialization milestones and up to \$800 million for the achievement of sales milestones. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales. We will achieve the next payment of up to \$60 million for the license of a medicine under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined the transaction price to be the \$25 million upfront payment we received when we entered into the collaboration. We allocated the transaction price to our single performance obligation. In the fourth quarter of 2019, we completed our R&D services performance obligation under this collaboration. We recognized revenue as we performed services based on our effort to satisfy our performance obligation relative to the total effort expected to satisfy our performance obligation. We completed our performance obligation earlier than we previously estimated, as a result, we recognized \$8.3 million of additional revenue in the fourth quarter of 2019. We do not have any remaining performance obligations under this collaboration. We will receive development and regulatory milestone payments from Biogen if Biogen advances the development candidate under this collaboration toward marketing approval.

Neurology Collaborations

2018 Strategic Neurology

In April 2018, we and Biogen entered into a strategic collaboration to develop novel antisense medicines for a broad range of neurological diseases and entered into a SPA. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for these diseases for 10 years. We are responsible for the identification of antisense drug candidates based on selected medicines. Biogen is responsible for conducting IND-enabling toxicology studies for the selected medicine. Biogen will have the option to license the selected medicine after it completes the IND-enabling toxicology study. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine.

In the second quarter of 2018, we received \$1 billion from Biogen, comprised of \$625 million to purchase our stock at an approximately 25 percent cash premium and \$375 million in an upfront payment. We are eligible to receive up to \$270 million in milestone payments for each medicine that achieves marketing approval. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales. We are advancing eight programs under this collaboration and from inception through December 2020, we have received \$1.05 billion in payments under this collaboration. We will achieve the next payment of \$7.5 million if we advance a program under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined our transaction price to be \$552 million, comprised of \$375 million from the upfront payment and \$177 million for the premium paid by Biogen for its purchase of our common stock. We determined the fair value of the premium we received by using the stated premium in the SPA and applying a lack of marketability discount. We included a lack of marketability discount in our valuation of the premium because Biogen received restricted shares of our common stock. We allocated the transaction price to our single performance obligation.

From inception through December 2020, we have included \$608 million in payments in the transaction price for our R&D services performance obligation under this collaboration, including \$11 million of milestone payments we achieved in 2020 and \$30 million of milestone payments we achieved in 2019. These milestone payments did not create new performance obligations because they are part of our original R&D services performance obligation. Therefore, we included these amounts in our transaction price for our R&D services performance obligation in the period we achieved the milestone payment. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation at the end of the contractual term in June 2028.

2013 Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license medicines resulting from this collaboration. We will usually be responsible for drug discovery and early development of antisense medicines and Biogen will have the option to license antisense medicines after Phase 2 proof-of-concept. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. We are currently advancing six investigational

medicines in development under this collaboration, including a medicine for Parkinson's disease (ION859), three medicines for ALS (tofersen, IONIS-C9_{Rx} and ION541), a medicine for multiple system atrophy (ION464) and a medicine for an undisclosed target. In the fourth quarter of 2018, Biogen exercised its option to license our most advanced ALS medicine, tofersen, our medicine in Phase 3 development for SOD1 ALS. As a result, Biogen is now responsible for global development, regulatory and commercialization activities and costs for tofersen.

Under the terms of the agreement, we received an upfront payment of \$100 million and are eligible to receive milestone payments, license fees and royalty payments for all medicines developed under this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately \$260 million in a license fee and milestone payments per program. The \$260 million per program consists of approximately \$60 million in development milestones, including amounts related to the cost of clinical trials, and up to \$130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any antisense medicines developed under this collaboration. From inception through December 2020, we have received over \$270 million in upfront fees, milestone payments and other payments under this collaboration. We will achieve the next payment of up to \$10 million if we advance a program under this collaboration.

At the commencement of our 2013 strategic neurology collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. At inception, we determined the transaction price to be the \$100 million upfront payment we received and allocated it to our single performance obligation. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. In the third quarter of 2019, we updated our estimate of the total effort we expect to expend to satisfy our performance obligation. As a result, we recorded a cumulative catch up adjustment of \$16.5 million to decrease revenue in the third quarter of 2019. During 2020, we completed our remaining research and development services and recognized the remaining revenue related to this performance obligation. From inception through the completion of our R&D services performance obligation in 2020, we included \$145 million in total payments in the transaction price for our R&D services performance obligation.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter we generated the payment because we did not have any performance obligations for the respective payment. The following are the payments we earned:

- In the third quarter of 2018, we earned a \$10 million milestone payment when Biogen initiated a Phase 1 study of IONIS-C9_{Rx}.
- In the fourth quarter of 2018, we earned a \$35 million license fee when Biogen licensed tofersen from us because Biogen had full use of the licenses without any continuing involvement from us.
- In the fourth quarter of 2018, we earned a \$5 million milestone when Biogen initiated a Proof-of-Concept study for tofersen.
- In the third quarter of 2019, we earned an \$8 million milestone payment when Biogen initiated a Phase 1/2 study of ION859 for the treatment of people with Parkinson's disease under this collaboration.
- In the fourth quarter of 2019, we earned a \$10 million milestone payment when Biogen advanced IONIS-C9_{Rx}.
- In the third quarter of 2020, we earned \$18 million in milestone payments when Biogen initiated a Phase 1/2 trial for ION464, an investigational medicine in development targeting alpha-synuclein to treat patients with multiple system atrophy.
- In the third quarter of 2020, we earned a \$10 million milestone payment when Biogen initiated a Phase 1/2 trial for ION541, an investigational medicine in development targeting ataxin 2 to treat patients with ALS.

2012 Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense medicines to treat neurodegenerative diseases. We are responsible for the development of each of the

medicines through the completion of the initial Phase 2 clinical study for such medicine. Biogen has the option to license a medicine from each of the programs through the completion of the first Phase 2 study for each program. Under this collaboration, we are currently advancing IONIS-MAPT_{Rx} for Alzheimer's disease and ION582 for Angelman syndrome. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. In the fourth quarter of 2019, Biogen exercised its option to license IONIS-MAPT_{Rx}. We are responsible for completing the Phase 1/2 in study patients with mild AD and a one-year long-term extension study. Biogen will have responsibility for global development, regulatory and commercialization activities and costs for IONIS-MAPT_{Rx}.

Under the terms of the agreement, we received an upfront payment of \$30 million. Over the term of the collaboration, we are eligible to receive up to \$210 million in a license fee and milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. The \$210 million per program consists of up to \$10 million in development milestone payments, plus a mark-up on the cost estimate of the Phase 1 and 2 studies and up to \$130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales of any medicines resulting from each of the three programs. From inception through December 2020, we have received \$154 million in payments under this collaboration, including \$19.5 million we received from Biogen for achieving milestones for advancing IONIS-MAPT_{Rx} during 2020. We will achieve the next payment of \$25 million if we continue to advance IONIS-MAPT_{Rx}.

Under our collaboration, we determined we had a performance obligation to perform R&D services. We allocated \$40 million in total payments to the transaction price for our R&D services performance obligation. In the third quarter of 2019, we completed our R&D services performance obligation when we designated a development candidate and Biogen accepted the development candidate. Biogen's decision to accept the development candidate was not within our control. We were recognizing revenue as we performed services based on our effort to satisfy our performance obligation relative to the total effort expected to satisfy our performance obligation. Because Biogen accepted the development candidate earlier than when we were previously estimating, we recognized \$6.3 million of accelerated revenue in the third quarter of 2019.

When we commenced development for IONIS-MAPT_{Rx} we identified our development work as a separate performance obligation. We are recognizing our IONIS-MAPT_{Rx} development performance obligation based on the percentage of completion. From inception through December 2020, we have included \$57 million in the transaction price for our IONIS-MAPT_{Rx} development performance obligation. We currently estimate we will satisfy our performance obligation in 2022. Our total transaction price for our IONIS-MAPT_{Rx} development performance obligation includes the following payments we achieved in 2019 and 2020 related to our development work:

- In the second quarter of 2019, we achieved a \$7.5 million milestone payment from Biogen when we advanced IONIS-MAPT_{Rx}.
- In the fourth quarter of 2019, we achieved a \$12 million milestone payment from Biogen when we entered into an agreement to conduct a long-term extension study for IONIS-MAPT_{Rx}.
- In the first quarter of 2020, we achieved a \$7.5 million milestone payment from Biogen when we advanced IONIS-MAPT_{Rx}.
- In the third quarter of 2020, we achieved a \$12 million milestone payment from Biogen when we advanced IONIS-MAPT_{Rx} in the long-term extension study for IONIS-MAPT_{Rx}.

In the fourth quarter of 2019, we identified another performance obligation upon Biogen's license of IONIS-MAPT_{Rx} because the license we granted to Biogen is distinct from our other performance obligations. We recognized the \$45 million license fee for IONIS-MAPT_{Rx} as revenue at that time because Biogen had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Biogen.

In the fourth quarter of 2019, we earned a \$10 million milestone payment when Biogen advanced ION582. We recognized this milestone payment in full in the fourth quarter of 2019 because we did not have any performance obligations related to this milestone payment.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Year Ended December 31,		
	2020	2019	2018
SPINRAZA royalties (commercial revenue)	\$286.6	\$293.0	\$237.9
R&D revenue	122.0	180.6	137.1
Total revenue from our relationship with Biogen	\$408.6	\$473.6	\$375.0
Percentage of total revenue	56%	42%	63%

Our consolidated balance sheet at December 31, 2020 and 2019 included deferred revenue of \$465.8 million and \$525.8 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

AstraZeneca

We have two collaborations with AstraZeneca, one focused on the treatment of cardiovascular, renal and metabolic diseases and a second focused on the treatment of oncology diseases. We and AstraZeneca are currently developing several investigational medicines under these collaborations, including medicines in development to treat people with cardiovascular disease, a genetically associated form of kidney disease, nonalcoholic steatohepatitis, or NASH, and cancer. From inception through December 2020, we have received more than \$380 million from our AstraZeneca collaborations.

Cardiovascular, Renal and Metabolic Diseases Collaboration

In July 2015, we and AstraZeneca formed a collaboration to discover and develop antisense therapies for treating cardiovascular, renal and metabolic diseases. Under our collaboration, AstraZeneca has licensed four medicines from us:

- ION449 (formerly IONIS-AZ4-2.5-L_{Rx}), an investigational medicine we designed to reduce the liver production of PCSK9 and lower the plasma level of LDL-C and thus reduce the risk of cardiovascular disease;
- ION532, an investigational medicine we designed to reduce the production of APOL1 for the treatment of APOL1-associated chronic kidney disease;
- ION839, an investigational medicine we designed to inhibit the production of PNPLA3 protein, a major genetic determinant of NASH progression; and
- ION455, an investigational medicine we designed as a potential treatment for NASH.

AstraZeneca is responsible for global development, regulatory and commercialization activities and costs for each of the medicines it has licensed and any medicines AstraZeneca licenses in the future.

Under the terms of the agreement, we received a \$65 million upfront payment. We are eligible to receive license fees and milestone payments of up to more than \$5.5 billion as medicines under this collaboration advance, including up to \$1.1 billion for the achievement of development milestones, up to \$2.9 billion for regulatory milestones and up to \$1.5 billion for commercial milestones. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. We will achieve the next payment of up to \$30 million under this collaboration if AstraZeneca advances a medicine under this collaboration. From inception through December 2020, we have received over \$235 million in upfront fees, license fees, milestone payments, and other payments under this collaboration, including \$30 million we earned in 2020 when AstraZeneca licensed ION455 and \$30 million in milestone payments we earned in 2020 when AstraZeneca advanced ION532 and ION449 in development.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for AstraZeneca. We determined the transaction price to be the \$65 million upfront payment we received and we allocated it to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy this performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy this performance

obligation in the third quarter of 2021. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. From inception through December 2020, we have included \$90 million in payments in the transaction price for our R&D services performance obligation.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. The following are the payments we have earned:

- In the first quarter of 2018, we earned two \$30 million license fees when AstraZeneca licensed ION532 and ION839 because AstraZeneca had full use of the licenses without any continuing involvement from us.
- In the third quarter of 2018, we earned a \$10 million milestone payment when AstraZeneca initiated a Phase 1 study of ION449.
- In the fourth quarter of 2019, we earned a \$10 million milestone payment when AstraZeneca initiated a Phase 1 study of ION839.
- In the first quarter of 2020, we earned a \$10 million milestone payment when AstraZeneca advanced ION532.
- In the fourth quarter of 2020, we earned a \$20 million milestone payment when AstraZeneca advanced ION449.
- In the fourth quarter of 2020, we earned a \$30 million license fee when AstraZeneca licensed ION455 because AstraZeneca had full use of the license without any continuing involvement from us.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense medicines to treat cancer. We and AstraZeneca also established an oncology research program. AstraZeneca has the option to license medicines resulting from the program, and if AstraZeneca exercises its option to license a medicine, it will be responsible for global development, regulatory and commercialization activities and costs for such medicine. In 2020, AstraZeneca licensed ION736, an investigational medicine in development targeting FOXP3 for the treatment of cancer.

Under the terms of this agreement, we received \$31 million in upfront payments. We are eligible to receive milestone payments and license fees up to more than \$265 million under this collaboration, including up to \$107 million for the achievement of development milestones and up to \$105 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. From inception through December 2020, we have received over \$140 million in upfront fees, milestone payments, and other payments under this oncology collaboration, including \$13 million we earned when AstraZeneca licensed ION736 in 2020. We will achieve the next payment of \$12 million if AstraZeneca advances ION736 in development.

We completed all of the performance obligations we identified under this collaboration in the first quarter of 2018.

Under this collaboration, we have also generated additional payments that we concluded were not part of other performance obligations discussed above. We recognized each of these payments in full in the respective quarter we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. The following are the payments we have earned:

- In the fourth quarter of 2018, we earned a \$17.5 million milestone payment and a \$10 million milestone payment when AstraZeneca advanced two programs under our collaboration.
- In the second quarter of 2020, we earned a \$13 million license fee when AstraZeneca licensed ION736 because AstraZeneca had full use of the license without any continuing involvement from us.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with AstraZeneca (in millions, except percentage amounts):

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
R&D revenue	\$88.0	\$28.1	\$120.7
Percentage of total revenue	12%	3%	20%

Our consolidated balance sheet at December 31, 2020 and 2019 included deferred revenue of \$10.0 million and \$25.0 million, respectively, related to our relationship with AstraZeneca.

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI_{Rx} for the prevention of thrombosis. We were responsible for completing a Phase 2 study of IONIS-FXI_{Rx} in people with end-stage renal disease on hemodialysis. Under the terms of the agreement, we received a \$100 million upfront payment in the second quarter of 2015. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI_{Rx} and to initiate development of IONIS-FXI-L_{Rx}, which Bayer licensed. In conjunction with the decision to advance these programs, we received a \$75 million payment from Bayer. In October 2019, Bayer decided it would advance IONIS-FXI-L_{Rx} following positive clinical results. Bayer is now responsible for all global development, regulatory and commercialization activities and costs for the FXI program.

We are eligible to receive up to \$385 million in license fees, milestone payments and other payments, including up to \$125 million for the achievement of development milestones and up to \$110 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of both medicines combined. From inception through December 2020, we have received over \$185 million from this collaboration. We will achieve the next payment of \$20 million if Bayer initiates a Phase 3 study for the FXI program.

At the commencement of this collaboration, we identified three performance obligations, the license of IONIS-FXI_{Rx}, R&D services and delivery of API, all of which we completed in 2016.

In February 2017, when we amended our collaboration with Bayer, we identified two new performance obligations, one for the license of IONIS-FXI-L_{Rx} and one for R&D services. We determined the transaction price to be the \$75 million payment. We allocated \$64.9 million to the license of IONIS-FXI-L_{Rx} based on its estimated relative stand-alone selling price and recognized the associated revenue upon our delivery of the license in the first quarter of 2017. We allocated \$10.1 million to our R&D services performance obligation based on an estimated relative stand-alone selling price. We recognized revenue for our R&D services performance obligation as we performed services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We completed our obligation in the third quarter of 2019.

In the fourth quarter of 2019, we earned a \$10 million milestone payment when Bayer decided it would advance IONIS-FXI-L_{Rx}. We recognized this milestone payment in full in the fourth quarter of 2019 because we did not have any performance obligations related to this milestone payment.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with Bayer (in millions, except percentage amounts):

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
R&D revenue	\$3.2	\$14.3	\$5.0
Percentage of total revenue	0%	1%	1%

Our consolidated balance sheet at December 31, 2020 did not include any deferred revenue related to our relationship with Bayer. Our consolidated balance sheet at December 31, 2019 included deferred revenue of \$2.4 million related to our relationship with Bayer.

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new medicines against targets for serious and rare diseases, including infectious diseases and some

conditions causing blindness. Under the terms of the agreement, we received upfront payments of \$35 million. Our collaboration with GSK currently includes two medicines targeting hepatitis B virus, or HBV: IONIS-HBV_{Rx} and IONIS-HBV-L_{Rx}. We designed these medicines to reduce the production of viral proteins associated with HBV infection. In the third quarter of 2019, following positive Phase 2 results, GSK licensed our HBV program. GSK is responsible for all global development, regulatory and commercialization activities and costs for the HBV program.

Under our agreement, if GSK successfully develops these medicines and achieves pre-agreed sales targets, we could receive license fees and milestone payments of up to \$262 million, including up to \$47.5 million for the achievement of development milestones, up to \$120 million for the achievement of regulatory milestones and up to \$70 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that GSK successfully commercializes under this alliance. From inception through December 2020, we have received more than \$190 million in payments under this alliance with GSK. We will achieve the next payment of \$15 million if GSK initiates a Phase 3 study of a medicine under this program.

We completed our R&D services performance obligations under our collaboration in the first quarter of 2015. We identified a new performance obligation when we granted GSK the license of the HBV program and assigned related intellectual property rights in the third quarter of 2019 because the license was distinct from our other performance obligations. We recognized the \$25 million license fee for the HBV program as revenue at that time because GSK had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to GSK.

We do not have any remaining performance obligations under our collaboration with GSK; however, we can still earn additional payments and royalties as GSK advances the HBV program.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with GSK (in millions, except percentage amounts):

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
R&D revenue	\$0.2	\$25.4	\$1.6
Percentage of total revenue	0%	2%	0%

We did not have any deferred revenue from our relationship with GSK at December 31, 2020 and 2019.

Janssen Biotech, Inc.

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense medicines that can be locally administered, including oral delivery, to treat autoimmune disorders of the GI tract. Under our collaboration, Janssen is currently advancing ION253 for the treatment of immune-mediated GI disease. Janssen licensed ION253 in the fourth quarter of 2017. Prior to Janssen’s license of ION253, we were responsible for the discovery activities to identify development candidates. Under the agreement, Janssen is responsible for global development, regulatory and commercialization activities and costs for ION253.

Under the terms of the agreement, we received \$35 million in upfront payments. We are eligible to receive up to more than \$285 million in license fees and milestone payments for these programs, including up to \$65 million for the achievement of development milestones, up to \$160 million for the achievement of regulatory milestones and up to \$60 million for the achievement of commercialization milestones. From inception through December 2020, we have received over \$80 million from this collaboration. In addition, we are eligible to receive tiered royalties up to the near teens on net sales from any medicines resulting from this collaboration. We will achieve the next payment of \$5 million if Janssen continues to advance ION253 in development.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Janssen. We determined the transaction price to be the \$35 million upfront payments we received. We allocated the \$35 million to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, which ended in the fourth quarter of 2017.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter in which we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. In the third quarter of 2020, we earned a \$5 million milestone payment when Janssen initiated a Phase 1 trial for ION253.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with Janssen (in millions, except percentage amounts):

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
R&D revenue	\$5.0	\$0.1	\$6.6
Percentage of total revenue	1%	0%	1%

We did not have any deferred revenue from our relationship with Janssen at December 31, 2020 and 2019.

Novartis

In January 2017, we initiated a collaboration with Novartis to develop and commercialize pelacarsen and IONIS-APOCIII-L_{Rx}. We received a \$75 million upfront payment in the first quarter of 2017. In the first quarter of 2019, Novartis licensed pelacarsen and we earned a \$150 million license fee. Novartis is responsible for conducting and funding future development and regulatory activities for pelacarsen, including a global Phase 3 cardiovascular outcomes study that Novartis initiated in the fourth quarter 2019. In connection with Novartis' license of pelacarsen, we and Novartis established a more definitive framework under which the companies would negotiate the co-commercialization of pelacarsen in selected markets. Included in this framework is an option by which Novartis could solely commercialize pelacarsen in exchange for Novartis paying us increased sales milestone payments based on sales of pelacarsen. When Novartis decided to not exercise its option for IONIS-APOCIII-L_{Rx}, we retained rights to develop and commercialize IONIS-APOCIII-L_{Rx}.

Under the collaboration, we are eligible to receive up to \$675 million in milestone payments, including \$25 million for the achievement of a development milestone, up to \$290 million for the achievement of regulatory milestones and up to \$360 million for the achievement of commercialization milestones. From inception through December 2020, we have received \$249 million in upfront payments, milestone payments, license fees and other payments from this collaboration. We are also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of pelacarsen. We will achieve the next payment of \$25 million if Novartis advances pelacarsen.

In conjunction with this collaboration, we entered into a SPA with Novartis. As part of the SPA, Novartis purchased 1.6 million shares of our common stock for \$100 million in the first quarter of 2017. As part of the SPA, Novartis was required to purchase \$50 million of Akcea's common stock at Akcea's IPO price or our common stock at a premium if an IPO did not occur by April 2018. Under the SPA, in the second quarter of 2017, Novartis purchased \$50 million of Akcea's common stock in a separate private placement concurrent with the completion of Akcea's IPO at a price per share equal to the IPO price.

At the commencement of this collaboration, we identified four separate performance obligations:

- R&D services for pelacarsen;
- R&D services for IONIS-APOCIII-L_{Rx};
- API for pelacarsen; and
- API for IONIS-APOCIII-L_{Rx}.

We determined that the R&D services for each medicine and the API for each medicine were distinct performance obligations.

We determined our transaction price to be \$108.4 million, comprised of the following:

- \$75 million from the upfront payment;
- \$28.4 million for the premium paid by Novartis for its purchase of our common stock at a premium in the first quarter of 2017; and
- \$5.0 million for the potential premium Novartis would have paid if they purchased our common stock in the future.

We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- \$64.0 million for the R&D services for pelacarsen;
- \$40.1 million for the R&D services for IONIS-APOCIII-L_{Rx};
- \$1.5 million for the delivery of pelacarsen API; and
- \$2.8 million for the delivery of IONIS-APOCIII-L_{Rx} API.

We recognized revenue related to each of the performance obligations as follows:

- We completed our R&D services performance obligation for pelacarsen in second quarter of 2019. As such, we recognized all revenue we allocated to the pelacarsen R&D services as of the end of the second quarter of 2019;
- We completed our R&D services performance obligation for IONIS-APOCIII-L_{Rx} in the fourth quarter of 2019 because Novartis elected to terminate the strategic collaboration for IONIS-APOCIII-L_{Rx} during the period. As a result, we were not required to provide any further R&D services, as such, we recognized all revenue allocated to the IONIS-APOCIII-L_{Rx} R&D services as of the end of the fourth quarter of 2019;
- We recognized the amount attributed to pelacarsen API when we delivered it to Novartis in 2017; and
- We recognized the amount attributed to IONIS-APOCIII-L_{Rx} API when we delivered it to Novartis in the second quarter of 2018.

We recognized revenue related to the R&D services for pelacarsen and IONIS-APOCIII-L_{Rx} performance obligations as we performed services based on our effort to satisfy our performance obligations relative to our total effort expected to satisfy our performance obligations.

During the years ended December 31, 2020 and 2019, we earned the following revenue from our relationship with Novartis (in millions, except percentage amounts):

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
R&D revenue	\$1.0	\$187.4	\$50.6
Percentage of total revenue	0%	17%	8%

We did not have any deferred revenue from our relationship with Novartis at December 31, 2020 and 2019.

Pfizer

In October 2019, we entered into a license agreement with Pfizer for vupanorsen, an investigational medicine in development to treat people with certain cardiovascular diseases. We completed a Phase 2 study of vupanorsen in patients with elevated levels of triglycerides, or hypertriglyceridemia, type 2 diabetes and NAFLD. Pfizer is responsible for all global development, regulatory and commercialization activities and costs for vupanorsen, subject to our right to co-commercialize in the U.S. and certain additional markets.

Under the terms of the agreement, we received a \$250 million upfront payment. We are also eligible to receive development, regulatory and sales milestone payments of up to \$1.3 billion, including up to \$205 million for the achievement of development milestones, up to \$250 million for the achievement of regulatory milestones and up to \$850 million for the achievement of commercialization milestones. From inception through December 2020, we have received over \$330 million, including a \$75 million milestone payment we earned in the fourth quarter of 2020 when Pfizer began the Phase 2b study of vupanorsen. We are also eligible to earn tiered royalties in the mid-teens to low

20 percent range on annual worldwide net sales. Prior to regulatory filing for marketing approval, we have the right, at our option to participate in certain commercialization activities with Pfizer in the U.S. and certain additional markets on pre-defined terms and based on meeting pre-defined criteria. We will achieve the next payment of \$50 million if Pfizer advances vupanorsen.

At the commencement of the license agreement, we identified three separate performance obligations:

- License of vupanorsen;
- R&D services for vupanorsen; and
- API for vupanorsen.

We determined the transaction price to be \$250 million, the upfront payment we received. We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- \$245.6 million for the license of vupanorsen;
- \$2.2 million for the R&D services for vupanorsen; and
- \$2.2 million for the delivery of vupanorsen API.

We are recognizing revenue related to each of our performance obligations as follows:

- We recognized \$245.6 million for the license of vupanorsen in the fourth quarter of 2019 because we determined the license we granted to Pfizer was distinct from our other performance obligations and Pfizer had full use of the license without any continuing involvement from us.
- We recognized revenue related to the R&D services for vupanorsen as we performed services based on our effort to satisfy our performance obligation relative to our total effort to satisfy our performance obligation. We completed our R&D services in mid-2020.
- We recognized the amount attributed to the API supply for vupanorsen when we delivered it to Pfizer in the fourth quarter of 2019.

In the fourth quarter of 2020, we earned a \$75 million milestone payment when Pfizer began the Phase 2b study of vupanorsen. We recognized this milestone payment in full in the fourth quarter of 2020 because we did not have any performance obligations related to this milestone payment.

During the years ended December 31, 2020 and 2019, we earned the following revenue from our relationship with Pfizer (in millions, except percentage amounts):

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
R&D revenue	\$82.1	\$248.7
Percentage of total revenue	11%	22%

We did not have any deferred revenue from our relationship with Pfizer at December 31, 2020. Our consolidated balance sheet at December 31, 2019 included deferred revenue of \$1.3 million related to our relationship with Pfizer.

PTC Therapeutics

In August 2018, we entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. Under the license agreement, we are eligible to receive up to \$26 million in payments. From inception through December 2020, we have received \$22 million from PTC. We are eligible to receive royalties from PTC in the mid-20 percent range on net sales in Latin America for each medicine. PTC's obligation to pay us royalties begins on the earlier of 12 months after the first commercial sale of a product in Brazil or the date that PTC recognizes revenue of at least \$10 million in Latin America.

In the third quarter of 2018 at the commencement of this collaboration, we identified two performance obligations, which were the licenses we granted to PTC to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. We recognized \$12 million in license fee revenue at that time because PTC had full use of both licenses without any continuing involvement from us. We do not have any remaining performance obligations under our collaboration with PTC. We can still earn additional payments and royalties as PTC commercializes TEGSEDI and WAYLIVRA.

Under this collaboration, we have also generated milestone payments that we concluded were not part of the performance obligations discussed above. We recognized each of these milestone payments in full in the respective quarter in which we achieved the milestone payment because the payments were distinct and we did not have any performance obligations for the respective payment. The following are the payments we have earned:

- In the second quarter of 2019, we earned a \$6 million payment when WAYLIVRA was approved by the EMA.
- In the fourth quarter of 2019, we earned \$4 million when TEGSEDI was approved in Brazil.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with PTC (in millions, except percentage amounts):

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
Licensing and other royalty revenue (commercial revenue)	\$1.6	\$10.2	\$12.0
Percentage of total revenue	0%	1%	2%

Our consolidated balance sheet at December 31, 2020 and 2019 did not include any deferred revenue related to our relationship with PTC.

Roche

Huntington's Disease

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for HD based on our antisense technology. Under the agreement, we discovered and developed tominersen, an investigational medicine targeting HTT protein in Phase 3 development. We developed tominersen through completion of our Phase 1/2 clinical study in people with early stage HD. In the fourth quarter of 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen. Roche is responsible for all global development, regulatory and commercialization activities and costs for tominersen.

Under the terms of the agreement, we received an upfront payment of \$30 million in April 2013 and an additional \$3 million payment in 2017. We are eligible to receive up to \$365 million in a license fee and milestone payments including up to \$70 million for the achievement of development milestones, up to \$170 million for the achievement of regulatory milestones and up to \$80 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to \$136.5 million in milestone payments for each additional medicine successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on any net sales of any product resulting from this alliance. From inception through December 2020, we have received \$150 million in upfront fees, milestone payments and license fees under this collaboration. We will achieve the next payment of \$15 million if Roche advances tominersen.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Roche. We determined the transaction price to be the \$30 million upfront payment we received and allocated it to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, which ended in the third quarter of 2017.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter in which we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. The following are the payments we have earned:

- In the fourth quarter of 2017, we earned a \$45 million license fee when Roche licensed tominersen because Roche had full use of the license without any continuing involvement from us.
- In the first quarter of 2019, we earned \$35 million in milestone payments when Roche dosed the first patient in the Phase 3 study of tominersen in the first quarter of 2019.

We do not have any remaining performance obligations related to tominersen under this collaboration with Roche; however, we can still earn additional payments and royalties as Roche advances tominersen.

IONIS-FB-L_{Rx} for Complement-Mediated Diseases

In October 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases. We are currently conducting Phase 2 studies in two disease indications for IONIS-FB-L_{Rx}, one for the treatment of patients with GA, the advanced stage of dry AMD, and a second for the treatment of patients with IgA nephropathy. Roche has the option to license IONIS-FB-L_{Rx} at the completion of these studies. Upon licensing, Roche will be responsible for global development, regulatory and commercialization activities and costs.

Under the terms of this agreement, we received a \$75 million upfront payment in the fourth quarter of 2018. We are eligible to receive up to \$684 million in development, regulatory and sales milestone payments and license fees. In addition, we are also eligible to receive tiered royalties from the high teens to 20 percent on net sales. We will achieve the next payment of \$20 million if we advance the Phase 2 study in patients with dry AMD.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Roche. We determined the transaction price to be the \$75 million upfront payment we received and allocated it to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. During the fourth quarter of 2020, we updated our estimate of the total effort we expected to expend to satisfy our performance obligation under this collaboration. In the fourth quarter of 2020, we recorded a cumulative catch up adjustment of \$9.2 million to decrease revenue because we updated our total cost estimate to complete the Phase 2 study of IONIS-FB-L_{Rx} for the treatment of patients with GA. We currently estimate we will satisfy our performance obligation in the fourth quarter of 2023.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
R&D revenue	\$5.9	\$57.0	\$8.3
Percentage of total revenue	1%	5%	1%

Our consolidated balance sheet at December 31, 2020 and 2019 included deferred revenue of \$47.2 million and \$52.3 million related to our relationship with Roche, respectively.

Other Agreement

Alnylam Pharmaceuticals, Inc.

Under the terms of our agreement with Alnylam, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a technology access fee, participation in fees from Alnylam’s partnering programs, as well as future milestone and royalty payments from Alnylam. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics. In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded antisense therapeutics, ssRNAi therapeutics, and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi

medicines targeting a limited number of therapeutic targets on a nonexclusive basis. Additionally, in 2015, we and Alnylam entered into an alliance in which we cross-licensed intellectual property. Under this alliance, we and Alnylam each obtained exclusive license rights to four therapeutic programs. Alnylam granted us an exclusive, royalty-bearing license to its chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against four targets, including FXI and Apo(a) and two other targets. In exchange, we granted Alnylam an exclusive, royalty-bearing license to our chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against four other targets. Alnylam also granted us a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for single-stranded antisense therapeutics. In turn, we granted Alnylam a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for double-stranded RNAi therapeutics.

In the fourth quarter 2020, we completed an arbitration process with Alnylam. The arbitration panel awarded us \$41.2 million for payments owed to us by Alnylam related to Alnylam's agreement with Sanofi Genzyme. We recognized the \$41.2 million payment from Alnylam as revenue in the fourth quarter of 2020 because we did not have any performance obligations for the respective payment.

	<u>Year Ended December 31,</u>		
	<u>2020</u>	<u>2019</u>	<u>2018</u>
R&D revenue	\$47.9	\$24.1	\$2.0
Percentage of total revenue	7%	2%	—

Our consolidated balance sheet at December 31, 2020 and 2019 did not include any deferred revenue related to our relationship with Alnylam.

7. Akcea Acquisition

Purchase Price and Direct Transaction Costs Accounting for the Akcea Acquisition

In October 2020, we acquired the shares of Akcea's common stock we did not own, increasing our ownership from 76 percent to 100 percent. Under the purchase agreement, we purchased 24.8 million shares at \$18.15 per share, resulting in a total purchase price of \$450.6 million.

To reflect our 100 percent ownership, we accounted for the increase in our ownership by eliminating the noncontrolling interest adjustment in stockholders' equity in accordance with the Consolidation accounting guidance (ASC Topic 810). We recognized the difference between the purchase price and the adjustment to noncontrolling interest in stockholders' equity as additional-paid-in capital. Refer to our *Statement of Stockholders' Equity* for detailed amounts.

We accounted for the transaction costs related to the Akcea Acquisition as a direct charge to stockholders' equity. We incurred \$40.6 million of direct transaction costs from the Akcea Acquisition, primarily comprised of banking and legal fees.

Equity Award Payouts related to the Akcea Acquisition

In October 2020, as part of the Akcea Acquisition, Ionis cancelled all of Akcea's equity awards. In exchange for the cancelled awards, if eligible under the terms of the Acquisition, we paid holder's a cash payment. We paid \$18.15 for each outstanding RSU. For each outstanding option with an exercise price less than \$18.15, we paid \$18.15 less the exercise price. As a result, we paid out \$53.4 million in the fourth quarter of 2020 related to Akcea's cancelled equity awards. We accounted for these payments as part of the transaction costs recorded to stockholders' equity in the fourth quarter of 2020. Because we did not replace the Akcea awards, we recognized all unrecognized non-cash stock-based compensation (\$59.3 million) under Akcea's Plan in our statement of operations in the post-acquisition period in the fourth quarter of 2020.

Severance and Retention Costs related to the Akcea Acquisition

As a result of the Akcea Acquisition, we expect to incur severance expenses of up to \$9.3 million and retention expenses of up to \$19.2 million. During the fourth quarter of 2020, we recorded \$15.3 million of severance and retention related costs in operating expenses. We will recognize the remaining severance and retention costs through October 2021.

The following table summarizes the costs by category related to the Akcea Acquisition (in millions):

	<u>Three Months Ended December 31, 2020</u>
R&D expenses	\$ 3.9
SG&A expenses	<u>11.4</u>
Total	<u>\$15.3</u>

The following table summarizes the severance and retention reserve included in accrued compensation for the period indicated related to Akcea Acquisition (in millions):

	<u>Three Months Ended December 31, 2020</u>
Severance & retention reserve beginning balance	\$ —
Severance & retention expensed during period	15.3
Amounts paid during the period	<u>(0.6)</u>
Severance & retention reserve ending balance	<u>\$14.7</u>

8. Severance and Retention Costs related to our Restructured European Operations

In the fourth quarter of 2020, we entered into a distribution agreement with Sobi to commercialize TEGSEDI and WAYLIVRA in Europe. Under the distribution agreement, Sobi took over all material distribution operations at the end of January 2021. We remain the marketing authorization holder for TEGSEDI and WAYLIVRA in Europe. We will continue to maintain limited European operations including regulatory, manufacturing, and the management of relationships with key opinion leaders. We will also continue to lead the TEGSEDI and WAYLIVRA global commercial strategy.

As a result of this change, we expect to incur up to \$14.8 million of severance and retention expenses. During the fourth quarter of 2020, we recorded \$12.5 million of severance and retention related costs in operating expenses related to this agreement. We will recognize the remaining expenses through October 2021, of which we will recognize the majority of the remaining expenses in the first quarter of 2021.

The following table summarizes the costs by category related to our restructured European operations (in millions):

	<u>Three Months Ended December 31, 2020</u>
R&D expenses	\$ 4.2
SG&A expenses	<u>8.3</u>
Total	<u>\$12.5</u>

The following table summarizes the severance and retention reserve included in accrued compensation for the periods indicated related to our restructured European operations (in millions):

	<u>Three Months Ended December 31, 2020</u>
Severance & retention reserve beginning balance	\$ —
Severance & retention expensed during period	12.5
Amounts paid during the period	<u>(0.1)</u>
Severance & retention reserve ending balance	<u>\$12.4</u>

9. Segment Information and Concentration of Business Risk

Through 2020, we had two reportable segments, our Ionis Core segment and Akcea Therapeutics. We have provided segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviewed to assess operating performance and to make operating decisions through 2020. Segment income (loss) from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment, we are exploiting our antisense technology to generate a broad pipeline of first-in-class and/or best-in-class medicines for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy.

Akcea was focused on developing and commercializing medicines to treat patients with serious and rare diseases. Akcea generated revenue from TEGSEDI and WAYLIVRA product sales and from its collaborations.

The following tables show our segment revenue and income (loss) from operations for 2020, 2019 and 2018 (in thousands), respectively.

2020	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	\$286,583	\$ —	\$ —	\$ 286,583
Product sales, net.	—	69,999	—	69,999
Licensing and other royalty revenue	11,334	—	(3,217)	8,117
Total commercial revenue	<u>297,917</u>	<u>69,999</u>	<u>(3,217)</u>	<u>364,699</u>
R&D revenue under collaborative agreements.	325,024	82,321	(42,780)	364,565
Total segment revenue.	<u>\$622,941</u>	<u>\$ 152,320</u>	<u>\$(45,997)</u>	<u>\$ 729,264</u>
Total operating expenses	<u>\$563,647</u>	<u>\$ 389,575</u>	<u>\$(51,876)</u>	<u>\$ 901,346</u>
Income (loss) from operations	<u>\$ 59,294</u>	<u>\$(237,255)</u>	<u>\$ 5,879</u>	<u>\$(172,082)</u>
2019	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	\$292,992	\$ —	\$ —	\$ 292,992
Product sales, net.	—	42,253	—	42,253
Licensing and other royalty revenue	12,616	10,172	(5,583)	17,205
Total commercial revenue	<u>305,608</u>	<u>52,425</u>	<u>(5,583)</u>	<u>352,450</u>
R&D revenue under collaborative agreements.	553,038	436,118	(219,007)	770,149
Total segment revenue.	<u>\$858,646</u>	<u>\$488,543</u>	<u>\$(224,590)</u>	<u>\$1,122,599</u>
Total operating expenses	<u>\$523,207</u>	<u>\$450,469</u>	<u>\$(216,960)</u>	<u>\$ 756,716</u>
Income (loss) from operations	<u>\$335,439</u>	<u>\$ 38,074</u>	<u>\$ (7,630)</u>	<u>\$ 365,883</u>
2018	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	\$237,930	\$ —	\$ —	\$237,930
Product sales, net.	—	2,237	—	2,237
Licensing and other royalty revenue	2,755	12,000	—	14,755
Total commercial revenue	<u>240,685</u>	<u>14,237</u>	<u>—</u>	<u>254,922</u>
R&D revenue under collaborative agreements.	401,259	50,630	(107,137)	344,752
Total segment revenue.	<u>\$641,944</u>	<u>\$ 64,867</u>	<u>\$(107,137)</u>	<u>\$599,674</u>
Total operating expenses	<u>\$380,212</u>	<u>\$ 295,683</u>	<u>\$ (14,849)</u>	<u>\$661,046</u>
Income (loss) from operations	<u>\$261,732</u>	<u>\$(230,816)</u>	<u>\$ (92,288)</u>	<u>\$(61,372)</u>

The following table shows our total assets by segment at December 31, 2020 and 2019 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
December 31, 2020	<u>\$2,792,222</u>	<u>\$435,824</u>	<u>\$(838,291)</u>	<u>\$2,389,755</u>
December 31, 2019	<u>\$3,478,081</u>	<u>\$599,250</u>	<u>\$(844,219)</u>	<u>\$3,233,112</u>

Contracts receivables at December 31, 2020 was comprised of approximately 99.5 percent from two significant partners. Contracts receivables at December 31, 2019 was comprised of approximately 75 percent from one significant partner.

10. Employment Benefits

We have employee 401(k) salary deferral plans covering all employees. Employees could make contributions by withholding a percentage of their salary up to the IRS annual limits of \$19,500 and \$26,000 in 2020 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately \$5.7 million, \$6.4 million and \$5.7 million in matching contributions for the years ended December 31, 2020, 2019 and 2018, respectively.

11. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If the potential loss from any legal proceeding is considered probable and the amount can be reasonably estimated, we accrue a liability for the estimated loss. Significant judgment is required to determine the probability of a loss and whether the amount of the loss is reasonably estimable. The outcome of any proceeding is not determinable in advance. As a result, the assessment of a potential liability and the amount of accruals recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding, and may revise our estimates.

On July 16, 2020, a purported stockholder of Akcea filed an action in the Delaware Court of Chancery captioned John Makris, et al. v. Stanley T. Croke, et al., C.A. No. 2020-0587, or the “Delaware Action.” The plaintiff in the Delaware Action asserts claims against (i) current and former members of Akcea’s board of directors; and (ii) Ionis, or collectively, the “Defendants”. The plaintiff asserts derivative claims on behalf of Akcea, which is a nominal defendant in the Delaware Action, as well as putatively direct claims on behalf of a purported class of Akcea’s stockholders. The plaintiff in the Delaware action asserts that the Defendants breached their fiduciary duties in connection with the licensing transaction that we and Akcea entered into regarding TEGSEDI and IONIS-TTR-L_{RX}. The plaintiff also asserts an unjust enrichment claim against Ionis. The plaintiff’s claims are similar to those asserted in a prior action in the Delaware Court of Chancery captioned City of Cambridge Retirement System v. Croke, et al., C.A. No. 2019-0905, which was dismissed with prejudice to the named plaintiff only on April 8, 2020. We believe that the claims asserted in the Delaware Action are without merit and anticipate filing a motion to dismiss the claims.

In light of the August 31, 2020 public announcement of the Akcea Acquisition, the parties to the Delaware Action entered into a stipulation whereby the Defendants need to respond to the complaint filed on July 16, 2020, and the plaintiff will file an amended complaint. The amended complaint has not yet been filed.

12. Fourth Quarter Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized fourth quarter data for 2020 and 2019 are as follows (in thousands, except per share data).

Three Months Ended December 31,	2020	2019
Revenue	\$ 290,281	\$493,680
Operating expenses	\$ 312,945	\$233,028
Income (loss) from operations	\$ (22,664)	\$260,652
Net income (loss)	\$(341,426)	\$203,957
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders . .	\$(340,271)	\$184,415
Basic net income (loss) per share ⁽¹⁾⁽²⁾	\$ (2.44)	\$ 1.31
Diluted net income (loss) per share ⁽¹⁾⁽³⁾	\$ (2.44)	\$ 1.28

(1) We compute net income (loss) per share independently for each quarter during the year.

(2) As discussed in Note 1, *Organization and Significant Accounting Policies*, we compute basic net income (loss) per share by dividing the total net income (loss) attributable to our common stockholders by our weighted-average number of common shares outstanding during the period. Our basic net income (loss) per share calculation for each of the fourth quarters in 2020 and 2019 considered our net income (loss) for Ionis on a stand-alone basis plus our share of Akcea's net loss for the period. To calculate the portion of Akcea's net loss attributable to our ownership, we multiplied Akcea's loss per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net income (loss) available to Ionis common stockholders for the calculation of net income (loss) per share is different than net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders in the consolidated statements of operations.

Our basic net income (loss) per share the quarter referenced was calculated as follows (in thousands, except per share amounts):

Three Months Ended December 31 , 2020	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Loss Per Share Calculation
Akcea's net loss in the pre-acquisition period attributable to our ownership	77,095	\$(0.05)	\$ (3,603)
Akcea's net loss in the post-acquisition period attributable to our ownership			(85,987)
Akcea's total net loss attributable to our ownership			\$ (89,590)
Ionis' stand-alone net loss			(250,682)
Net loss available to Ionis common stockholders			\$(340,272)
Weighted average shares outstanding			139,956
Basic net loss per share			\$ (2.44)

Three Months Ended December 31 , 2019	Weighted Average Shares Owned in Akcea	Akcea's Net Income Per Share	Basic Net Income Per Share Calculation
Common shares	71,342	\$0.87	\$ 62,243
Akcea's net income attributable to our ownership.			\$ 62,243
Ionis' stand-alone net income.			121,552
Net income available to Ionis common stockholders			\$183,795
Weighted average shares outstanding			140,583
Basic net income per share			\$ 1.31

- (3) We had net income available to Ionis common stockholders for the fourth quarter of 2019. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period as follows (in thousands except per share amounts):

<u>Three Months Ended December 31, 2019</u>	<u>Income (Numerator)</u>	<u>Shares (Denominator)</u>	<u>Per- Share Amount</u>
Net income available to Ionis common stockholders.	\$183,795	140,583	\$1.31
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,467	
Shares issuable upon restricted stock award issuance	—	848	
Shares issuable related to our ESPP	—	18	
Shares issuable related to our 0.125 percent convertible notes	644	860	
Shares issuable related to our 1 percent convertible notes	<u>12,046</u>	<u>9,527</u>	
Income available to Ionis common stockholders, plus assumed conversions.	<u>\$196,485</u>	<u>153,303</u>	<u>\$1.28</u>



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