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, 2019

☐ **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	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)
2855 Gazelle Court, Carlsbad, CA	**92010**
(Address of Principal Executive Offices)	(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. (Check one):

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 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 $7,483,343,134 as of June 30, 2019.*

The number of shares of voting common stock outstanding as of February 20, 2020 was 139,219,800.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 29, 2020 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 4, 2020 are incorporated by reference into Part III of this Report.

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* Excludes 23,957,052 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, 2019. 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 majority-owned affiliate. 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, 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.

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. 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. 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. 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.

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. At December 31, 2019, we owned approximately 76 percent of Akcea's stock.

IONIS PHARMACEUTICALS, INC.
FORM 10-K
For the Fiscal Year Ended December 31, 2019
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PART I

Item 1. Business

Overview

We are a leader in discovering and developing RNA-targeted therapeutics. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics that we believe has fundamentally changed medicine and transformed the lives of people with devastating diseases. Our large, diverse and advancing pipeline has over 40 potential first-in-class and/or best-in-class medicines designed to address a broad spectrum of therapeutic areas, such as neurodegenerative diseases, cardiometabolic diseases, cancer and others. The medicines in our pipeline address patients with diseases ranging from rare to common.

In 2019, we achieved important goals across our business, including advancing four new medicines into pivotal studies. We also reported positive clinical proof-of-concept results from five medicines, four of which were LICA medicines. We advanced and grew our pipeline of unpartnered medicines, which we call our Ionis-owned pipeline. In addition, we made significant progress across the rest of our pipeline by advancing numerous medicines into earlier stages of development, six of which were Ionis-owned medicines. In 2019, we also broadened the scope of our antisense technology by investing in complementary technologies such as new LICA strategies to address more organ systems and cell types and technologies to potentially identify novel targets to ensure continued pipeline growth. These accomplishments enabled us to achieve revenues in excess of $1.1 billion, net income of nearly $300 million and a year-end cash balance of $2.5 billion.

This year we plan to use our financial strength to invest fully in those areas of the business that we believe have the greatest potential to create value for patients and shareholders. By the end of this year, we plan to have six pivotal studies underway and report clinical proof-of-concept data for six or more medicines. We also plan to expand the reach of our antisense technology by optimizing additional routes of administration, such as oral and pulmonary for which we expect clinical data this year. Additionally, this year, we are continuing to prioritize the growth and advancement of our Ionis-owned pipeline. Building on our achievements in 2019, we believe that continued advances in our pipeline and technology will enable us to achieve our goal of 10 or more new drug applications through the end of 2025.

Our goal is to determine the optimal development and commercialization strategy for each medicine in our pipeline, while ensuring we remain focused on innovation and delivering substantial value for patients in need and shareholders. With this goal firmly in mind, this year we plan to further develop our commercial strategy and capabilities to ensure we maximize the value of each of our medicines.

By building on our strong foundation and continuing to focus on our strategic priorities, we believe we are achieving our vision of becoming one of the most successful and innovative companies in the healthcare industry. We intend to continue to pursue our vision by executing on our strategic priorities: advancing our Ionis-owned pipeline, further developing our commercial strategies and capabilities, and expanding the reach of our antisense technology.

We have three commercial medicines approved in major markets around the world, SPINRAZA, TEGSEDI and WAYLIVRA. We have four drugs in pivotal studies, tominersen (formerly IONIS-HTT_{Rx}) for Huntington's disease, tofersen for SOD1-ALS, AKCEA-APO(a)-L_{Rx} for cardiovascular disease, or CVD, and AKCEA-TTR-L_{Rx} for all forms of TTR amyloidosis, or ATTR. Our goal is to start up to five additional pivotal studies before the end of 2021.

SPINRAZA is a 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, 2019, more than 10,000 patients were on SPINRAZA therapy in markets around the world. Additionally, as of December 31, 2019, SPINRAZA is approved in over 50 countries with formal reimbursement in 40 countries. Through December 31, 2019, we have earned more than $1 billion in revenues from our SPINRAZA collaboration, including more than $640 million in royalties on sales of SPINRAZA.

TEGSEDI, a once weekly, self-administered subcutaneous medicine, was approved in 2018 in the U.S., EU and Canada for the treatment of patients with polyneuropathy caused by hereditary TTR amyloidosis, or hATTR, a debilitating, progressive, and fatal disease. Akcea, our majority-owned affiliate focused on developing and commercializing medicines to treat patients with serious and rare diseases, launched TEGSEDI in the U.S. and EU in late 2018. TEGSEDI is commercially available in more than 10 countries. Akcea plans to expand the global launch of TEGSEDI by launching in additional countries. In Latin America, PTC Therapeutics, or PTC, through its exclusive license from Akcea, is launching TEGSEDI in Brazil and is working towards access in additional Latin American countries.

WAYLIVRA, a once weekly, self-administered, subcutaneous medicine, received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. Akcea launched WAYLIVRA in the EU in the third quarter of 2019 and is leveraging its existing commercial infrastructure in Europe to market WAYLIVRA. PTC through its exclusive license agreement with Akcea is working to expand access to WAYLIVRA across Latin America, beginning in Brazil with potential approval in 2020.

As a result of our business achievements, we generated more than $1 billion in revenues in 2019 and $294 million of net income. We earned $352 million of commercial revenue and $770 million in research and development revenue, including significant license fees for two LICA medicines. First, we earned a $150 million license fee from Novartis when Akcea licensed AKCEA-APO(a)-L_{Rx} in the first quarter of 2019. Additionally, in the fourth quarter of 2019, Akcea initiated a collaboration with Pfizer for the license of AKCEA-ANGPTL3-L_{Rx} to treat people with cardiovascular and metabolic diseases. Akcea received a $250 million upfront license fee, of which we recognized nearly all into revenue in the fourth quarter of 2019.

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 is a global foundation-of-care for the treatment of patients of all ages with SMA. Biogen, our partner responsible for commercializing SPINRAZA worldwide, reported that as of December 31, 2019, more than 10,000 patients were on SPINRAZA therapy in markets around the world. Additionally, as of December 31, 2019, SPINRAZA is approved in over 50 countries with formal reimbursement in 40 countries.

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 forms of the disease. 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 OLE study for patients with SMA who participated in prior SPINRAZA studies.

For over five 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) treated pre-symptomatically.

Biogen is also 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. We and Biogen believe that the favorable safety and tolerability profile of SPINRAZA that has been observed in over 10,000 patients now on SPINRAZA treatment supports the potential to evaluate higher dosing. Biogen plans to enroll SMA patients of all ages, including adults, in the DEVOTE study.

In all clinical studies, SPINRAZA demonstrated a favorable safety profile. The most common side effects of SPINRAZA included lower respiratory infection, fever, constipation, headache, vomiting, back pain, and post-lumbar puncture syndrome. For additional safety information, please see www.spinraza.com (Any information that is included on or linked to this website is not part of this report or any registration statement or report that incorporates this report by reference).

TEGSEDI – TEGSEDI (inotersen) injection is an RNA-targeted medicine designed to reduce the production of TTR protein that we licensed to Akcea in March 2018.

TEGSEDI is commercially available in more than 10 countries. Akcea plans to expand the global launch of TEGSEDI, by launching in additional countries. In Latin America PTC is launching TEGSEDI in Brazil and is working towards access in additional Latin American countries. The FDA approved TEGSEDI for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults in October 2018. TEGSEDI is also approved in the EU, Canada and Brazil for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis.

TTR amyloidosis that is the result of inherited mutations in the *TTR* gene is referred to as hereditary ATTR, or 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 the tissues, such as peripheral nerves, heart, gastrointestinal system, eyes, kidneys, central nervous system, thyroid and bone marrow. The presence of TTR 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.

Polyneuropathy due to hATTR is caused by the accumulation of misfolded mutated TTR protein in the peripheral nerves. People with polyneuropathy due to hATTR experience ongoing debilitating nerve damage throughout their body resulting in the progressive loss of sensation in the extremities that advances centrally, and loss of motor functions, such as walking. These people also accumulate TTR in other major organs, which progressively compromises their function and eventually leads to death within five to 15 years of disease onset.

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. It is estimated that more than 200,000 people worldwide have wt-ATTR. 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.

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 identified thrombocytopenia and safety signals related to renal function during the study. We implemented enhanced monitoring during the study to support early detection and management of these issues. Serious platelet and renal events were infrequent and manageable with routine monitoring, which has proven effective since implementation.

We are also conducting an ongoing OLE study in patients with hATTR treated with TEGSEDI. This study is intended to evaluate the long-term efficacy and safety profile of TEGSEDI. We have observed that the benefits TEGSEDI demonstrated in the NEURO-TTR study continued in the OLE.

The product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis and requires periodic blood and urine monitoring. TEGSEDI has a Risk Evaluation and Mitigation Strategy, or REMS, program. For TEGSEDI's full prescribing information, including boxed warnings, please see www.tegsedi.com (Any information that is included on or linked to this website is not part of this report or any registration statement or report that incorporates this report by reference).

WAYLIVRA – WAYLIVRA (volanesorsen) is an antisense medicine designed to treat people with rare, hereditary diseases characterized by extremely elevated triglyceride levels and a high risk of life-threatening pancreatitis, such as FCS and familial partial lipodystrophy, or FPL, that we licensed to Akcea.

Akcea launched WAYLIVRA in the EU in the third quarter of 2019 and is leveraging its existing commercial infrastructure in Europe to market WAYLIVRA. Akcea also plans to launch WAYLIVRA in Latin America through its exclusive license agreement with PTC if WAYLIVRA is approved by ANVISA. WAYLIVRA received conditional marketing authorization from the EC in May 2019 as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis. In August 2019, Akcea launched WAYLIVRA in Germany and preparations are underway to launch in additional countries this year.

In August 2018, we received a complete response letter, or CRL, from the Division of Metabolism and Endocrinology Products of the FDA regarding the NDA for WAYLIVRA. In November 2018, we received a Notice of Noncompliance withdrawal letter, or NON-W, from Heath Canada for WAYLIVRA. Our goal is to refile the NDA for WAYLIVRA with the FDA this year.

FCS and FPL, are each 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 as a result of these patients' severely elevated blood triglyceride levels. In addition, people with FCS are often unable to work, adding to their disease. 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. People with FPL typically have diabetes and other metabolic abnormalities, including elevated triglycerides, which increases their risk of pancreatitis.

WAYLIVRA acts to reduce 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 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 and 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.*

The most common adverse events in the APPROACH study were injection site reactions and reductions in platelet levels. For important safety information for WAYLIVRA, including method of administration, special warnings, drug interactions and adverse drug reactions, please see the European Summary of Product Characteristics at: www.waylivra.eu. (Any information that is included on or linked to this website is not part of this report or any registration statement or report that incorporates this report by reference).

In August 2019, we reported top line results from the BROADEN study of WAYLIVRA in FPL. BROADEN is a randomized, double blind, placebo-controlled study of 300mg of WAYLIVRA administered by a subcutaneous injection in patients with FPL. In the study, WAYLIVRA met its primary endpoint demonstrating a statistically significant reduction in triglyceride levels. WAYLIVRA also met a key secondary endpoint with a statistically significant reduction in liver fat. The most common adverse events observed in WAYLIVRA-treated patients were mild or moderate in severity and included injection site reactions, cold-like symptoms, urinary tract infection, and reductions in platelet levels. Patients in the BROADEN study were also eligible to enroll into an OLE study upon completing dosing in the pivotal study.

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.

See our separate section below where we further discuss Akcea, our majority-owned affiliate focused on developing and commercializing medicines to treat people with serious and rare diseases.

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 also can 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 DNA/genes to the protein making complex in the cell. When our 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

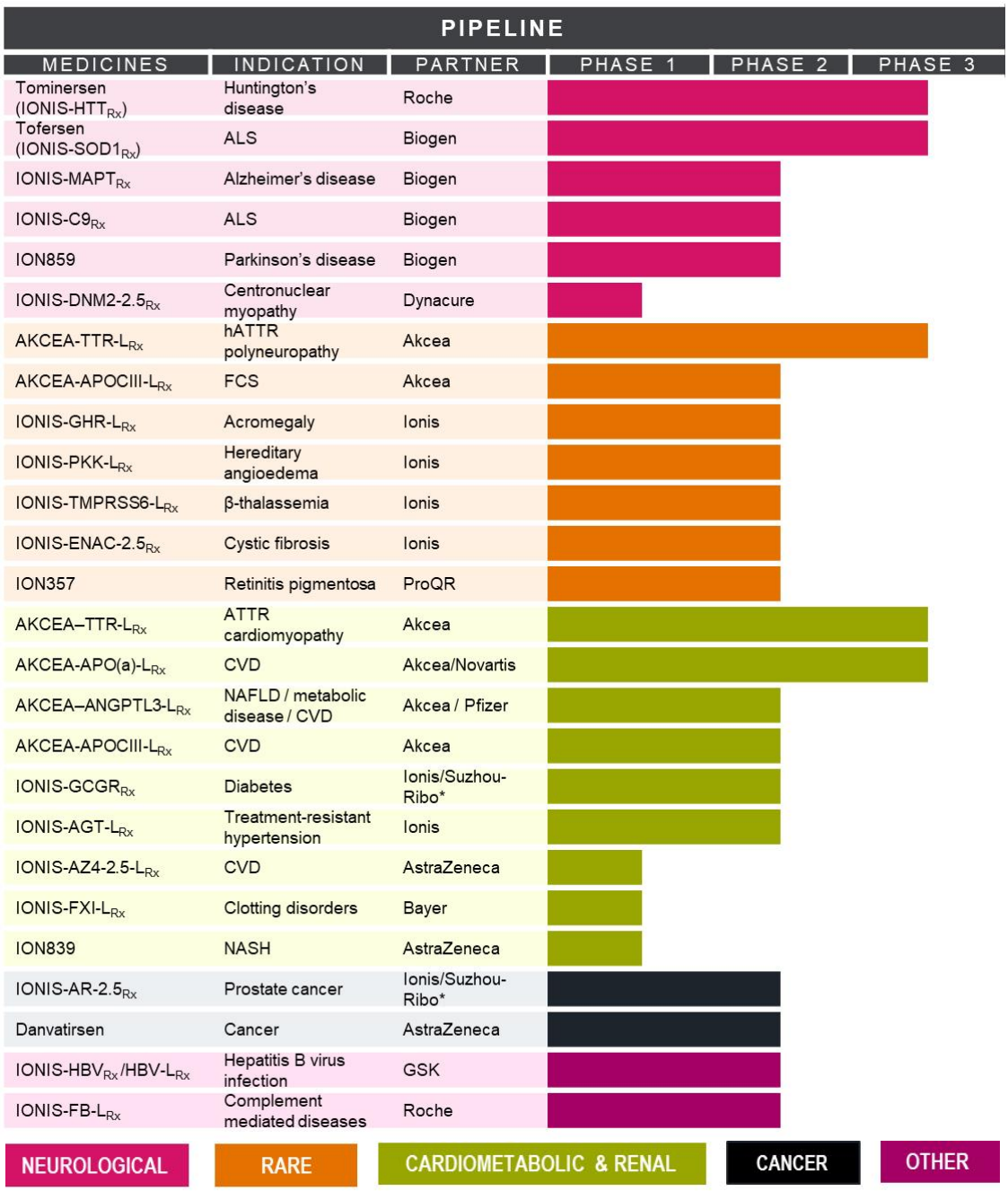
We are a leader in the discovery and development of an exciting class of RNA-targeted medicines called antisense oligonucleotide, or ASO, medicines, or just antisense medicines. With our proprietary drug discovery platform, we can rapidly identify medicines from a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas in which our medicines will work best, efficiently screening many targets in parallel and carefully selecting the best candidates. By combining this efficiency with our rational approach to selecting disease targets, we have built a large and diverse portfolio of medicines we designed to treat a variety of health conditions, such as cardiometabolic diseases, neurodegenerative diseases, cancer, rare 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, building a broad proprietary portfolio of medicines to treat many diseases and 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 19 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 up to 30-fold for liver targets, compared to non-conjugated antisense medicines. We currently have 16 LICA medicines in development, including two LICA medicines currently in Phase 3 studies, AKCEA-APO(a)-L_{Rx}, for CVD and AKCEA-TTR-L_{Rx}, for all forms of ATTR. 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 for all of 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.



* China rights only

The above table lists the medicines in our clinical pipeline. The table includes the disease indication, a partner (if the medicine is partnered), and the development status of each medicine.

Focusing on our key fundamental strategies has created a deep and broad pipeline of over 40 potentially first-in-class and/or best-in-class medicines that we believe 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. With a pipeline as large and advanced as ours, we have a number of clinical events each year as we initiate new clinical studies, complete and report data from clinical studies, and add numerous new medicines to our pipeline.

Our Phase 3 Medicines

As of the end of 2019, we have four medicines in pivotal Phase 3 studies: tominersen, tofersen, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx}.

			PHASE 3		
MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
Tominersen (IONIS-HTT_{Rx})	Huntington's disease	Roche			
Tofersen (IONIS-$SOD1_{Rx}$)	ALS	Biogen			
AKCEA-TTR-L_{RX}	ATTR	Akcea			
AKCEA-APO(a)-L_{Rx} (TQJ230)	CVD	Novartis			

Tominersen (IONIS-HTT_{Rx} or RG6042**) –** Tominersen is an 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., there are approximately 30,000 individuals with symptomatic HD and more than 200,000 people at risk of inheriting HD. The prevalence of HD is similar in other parts of the world. HD is a triplet repeat disorder and is one of a large family of genetic diseases in which the body mistakenly repeats certain gene sequences. 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 and tominersen demonstrated a favorable safety and tolerability profile. 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. The results from this study were the first 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 a broad clinical program including multiple studies of tominersen. Roche initiated a Phase 3 GENERATION HD1 study of tominersen. GENERATION HD1 is a randomized, multicenter, double-blind, 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 natural 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.

In August 2018, 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 licensing option to develop and commercialize tominersen following the completion of a Phase 1/2 randomized, placebo-controlled, dose escalation study of tominersen in people with HD. Roche is responsible for all tominersen development, regulatory and commercialization activities and costs.

Tofersen (IONIS-SOD1$_{Rx}$ or BIIB067**) –** Tofersen is an 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. ALS is a rare, fatal, neurodegenerative disorder. People with ALS suffer progressive degeneration of the motor neurons, which results in a declining quality of life and ultimately death. The second most common familial form of ALS is SOD1-ALS, in which people have a mutation in the *SOD1* gene that causes a progressive loss of motor neurons. As a result, people with SOD1-ALS experience muscle weakness, loss of movement, difficulty breathing and swallowing and eventually succumb to the disease. Currently, treatment options for people with 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, or ALSFRS, 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 safety and tolerability profile in this study supported the continued development of tofersen in ALS.

In March 2019, Biogen initiated and dosed the first patient in the VALOR Phase 3 clinical study of tofersen. VALOR is assessing the efficacy and safety of tofersen versus placebo. The primary endpoint of this study is an analysis based on the ALSFRS, which is a validated rating instrument that monitors the progression of disability in patients with ALS.

In December 2018, Biogen exercised its licensing option to develop and commercialize tofersen based on the positive interim analysis from the Phase 1/2 study. Following its licensing, Biogen is responsible for all tofersen development, regulatory and commercialization activities and costs.

AKCEA-TTR-L$_{Rx}$ – AKCEA-TTR-L$_{Rx}$ is a 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 co-developing AKCEA-TTR-L$_{Rx}$ with Akcea for the treatment of people with all forms of TTR amyloidosis as a once monthly self-administered subcutaneous injection. 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 AKCEA-TTR-L$_{Rx}$ in healthy volunteers at the Heart Failure Society of America Annual Meeting. In this study, subjects treated with AKCEA-TTR-L$_{Rx}$ achieved dose-dependent reductions of TTR protein of up to 94 percent and AKCEA-TTR-L$_{Rx}$ demonstrated a favorable safety and tolerability profile, consistent with our other liver LICA medicines. There were no serious adverse events in AKCEA-TTR-L$_{Rx}$ treated-subjects and no dosing interruptions due to an adverse event.

We and Akcea are evaluating AKCEA-TTR-L$_{Rx}$ in a broad Phase 3 program. 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 AKCEA-TTR-L$_{Rx}$ in November 2019. NEURO-TTRansform is a multi-center, randomized, open-label study designed to evaluate the efficacy and safety of AKCEA-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 was completed in 2017. The NEURO-TTRansform study includes multiple primary endpoints, including the percent change from baseline in serum TTR concentration, the change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7), and the change from baseline in Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN).

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

AKCEA-APO(a)-L_{Rx} (TQJ230) **–** AKCEA-APO(a)-L_{Rx} is a LICA medicine we designed to inhibit the production of apolipoprotein(a), or Apo(a), protein in the liver to offer a direct approach for reducing lipoprotein(a), or Lp(a). AKCEA-APO(a)-L_{Rx} inhibits the production of the Apo(a) protein, thereby reducing Lp(a). Elevated Lp(a) is recognized as an independent, genetic cause of CVD. 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.

Lp(a) is difficult to inhibit using other technologies, such as small molecules and antibodies. There are multiple genetically determined forms of the Apo(a) molecule and creating a small molecule or antibody that can interact with multiple targets is difficult. 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 lipid-focused treatment.

We reported results of the Phase 2 study with AKCEA-APO(a)-L_{Rx} 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, the recognized threshold for risk of CVD. This study of AKCEA-APO(a)-L_{Rx} was the longest and largest clinical study in patients with established CVD and elevated levels of Lp(a). This study was also the longest and largest clinical study of any of our LICA medicines. AKCEA-APO(a)-L_{Rx} demonstrated a favorable safety and tolerability profile in the study. Compliance in the study was almost 90 percent, which was higher than what we observed in the placebo group.

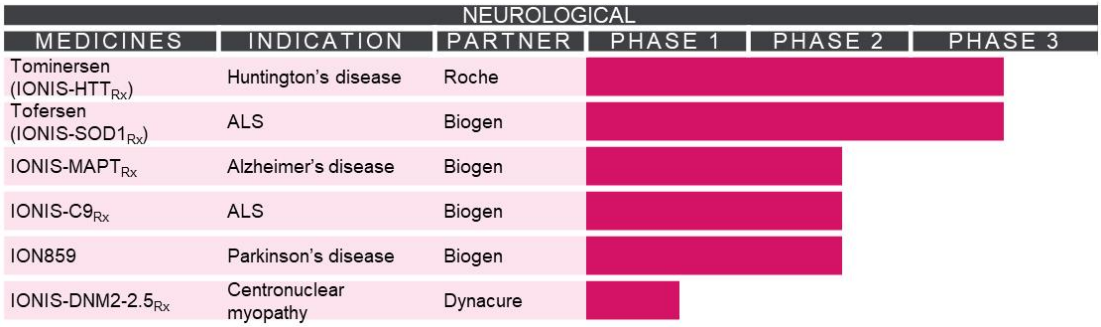
Akcea initiated a collaboration with Novartis in January 2017 to advance AKCEA-APO(a)-L_{Rx}. In February 2019, Novartis exercised its licensing option to develop and commercialize AKCEA-APO(a)-L_{Rx}. Following its licensing, Novartis is responsible for all AKCEA-APO(a)-L_{Rx} development, regulatory and commercialization activities and costs.

In December 2019, Novartis initiated the Phase 3 Lp(a)HORIZON study of AKCEA-APO(a)-L_{Rx}, a global, randomized, double-blinded, placebo-controlled outcomes study in approximately 7,500 patients with elevated Lp(a) levels and a prior cardiovascular event. Patients will be treated with 80 mg of AKCEA-APO(a)-L_{Rx} 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.

Neurological Disease Medicines in Development

We are discovering and developing antisense medicines to treat people with inadequate treatment options for neurological diseases. 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 have multiple investigational medicines in clinical trials for rare neurological diseases. 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



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

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

IONIS-MAPT$_{Rx}$ (BIIB080) – IONIS-MAPT$_{Rx}$ is an 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.

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 and non-neuronal cells 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. AD generally occurs late in life and may progress to death in five to 20 years after the onset of the disease. FTD has a more rapid disease progression. There are approximately five million people living with AD in the U.S. and approximately 55,000 people affected by FTD in the U.S.

We and Biogen are evaluating IONIS-MAPT$_{Rx}$ in a Phase 1/2 double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the safety and activity of once-monthly intrathecal injections of IONIS-MAPT$_{Rx}$ in patients with mild AD. In January 2020, we completed enrollment in the Phase 1/2 study of IONIS-MAPT$_{Rx}$.

In December 2019, Biogen exercised its licensing option to develop and commercialize IONIS-MAPT$_{Rx}$. We are responsible for completing the Phase 1/2 in study patients with mild AD that we initiated in 2017 and a one-year long-term extension study that began in 2019. Biogen will have responsibility for all other studies and any further development, including regulatory and commercialization activities and costs.

IONIS-C9$_{Rx}$ (BIIB078) – IONIS-C9$_{Rx}$ is an 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, the most prevalent genetic cause of ALS worldwide. There is substantial evidence that this mutation can lead to rapid progressive loss of motor neurons in people with C9ORF72-ALS. This 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 familial form of ALS. The first is tofersen, designed to treat SOD1 related ALS, caused by a mutation in the *SOD1* gene.

ION859 (BIIB094) – ION859 is an 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 exact cause of PD is unknown, but it is believed to be a combination of genetics and environmental factors. There are known hereditary mutations in the *LRRK2* gene that cause Parkinson's disease. The most common genetic mutation associated with PD is found in the *LRRK2* gene. 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, we 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.

IONIS-DNM2-2.5$_{Rx}$ (DYN101) – IONIS-DNM2-2.5$_{Rx}$ is a Generation 2.5 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 congenital myopathies where cell nuclei are abnormally located in the center of the skeletal muscle cells. It is characterized by muscle weakness, decreased muscle tone and muscle atrophy, ranging from severe to mild.

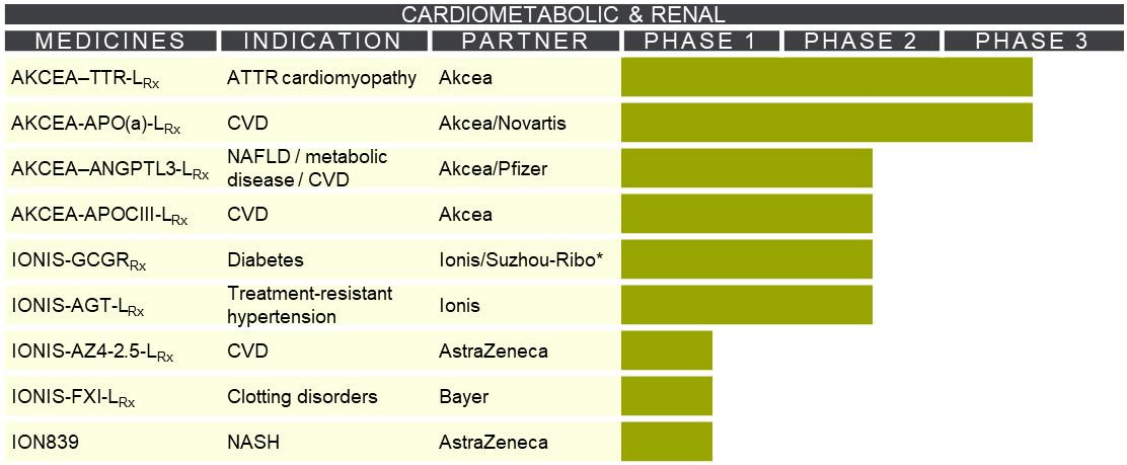
DNM2 reduction demonstrated improved muscle mass and muscle force, and extended lifespan in animal models of the most severe form of CNM.

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 in 18 patients who are 16 years of age or older and is designed to assess the safety and tolerability of multiple doses of IONIS-DNM2-2.5$_{Rx}$ administered intravenously.

Cardiometabolic and Renal Disease Medicines in Development

CVD is an important area of focus for us. According to the World Health Organization, or WHO, CVD was 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 key components of cardiovascular disease, including various atherogenic lipids, inflammation and thrombosis. Metabolic disorders, such as diabetes and nonalcoholic steatohepatitis, or NASH, are chronic diseases that affect tens of millions of people. According to the Centers for Disease Control and Prevention, diabetes affects more than 30 million people in the U.S., or nine percent of the population, with type 2 diabetes constituting 90 percent of those cases. 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 and Renal Disease Clinical Pipeline



AKCEA-TTR-L$_{Rx}$ – See the medicine description under "Our Phase 3 Medicines" section above.

AKCEA-APO(a)-L$_{Rx}$ – See the medicine description under "Our Phase 3 Medicines" section above.

AKCEA-ANGPTL3-L$_{Rx}$ – AKCEA-ANGPTL3-L$_{Rx}$ is a 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 AKCEA-ANGPTL3-L$_{Rx}$ 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 AKCEA-ANGPTL3-L$_{Rx}$ 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, AKCEA-ANGPTL3-L$_{Rx}$ demonstrated a favorable safety and tolerability profile.

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 AKCEA-ANGPTL3-L$_{Rx}$ administered weekly and monthly. AKCEA-ANGPTL3-L$_{Rx}$ achieved statistically significant, dose-dependent reductions in the study's primary endpoint of fasting triglycerides compared to placebo at all dose levels. AKCEA-ANGPTL3-L$_{Rx}$ 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. AKCEA-ANGPTL3-L$_{Rx}$ demonstrated a favorable safety and tolerability profile in the study.

In October 2019, we exclusively licensed AKCEA-ANGPTL3-L$_{Rx}$ to Pfizer. Pfizer is responsible for all development and regulatory activities and costs beyond those associated with the above Phase 2 study. Akcea has 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.

AKCEA-APOCIII-L$_{Rx}$ – AKCEA-APOCIII-L$_{Rx}$ is a 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, a rare, hereditary disease characterized by extremely elevated triglyceride levels, are at high risk for acute pancreatitis and other serious conditions. ApoC-III is also the target of WAYLIVRA, 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 and Akcea plan to initiate a Phase 3 study this year 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 and patient convenience by allowing for significantly lower doses and less frequent administration, compared to WAYLIVRA.

In October 2017, we reported positive results of a Phase 1/2 clinical study in healthy volunteers with elevated triglyceride levels. Patients in the study were treated with multiple doses at either weekly or monthly dosing intervals. Patients treated with AKCEA-APOCIII-L_{Rx} demonstrated significant dose-dependent reductions in apoC-III protein and triglycerides. In this study, AKCEA-APOCIII-L_{Rx} demonstrated a favorable safety and tolerability profile. No serious adverse events, platelet count reductions, changes in liver function or adverse events leading to treatment discontinuation were observed.

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 AKCEA-APOCIII-L_{Rx} administered weekly, bi-weekly, or monthly. AKCEA-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, more than 90 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. AKCEA-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. AKCEA-APOCIII-L_{Rx} demonstrated a favorable safety and tolerability profile in the study.

IONIS-GCGR$_{Rx}$ – IONIS-GCGR$_{Rx}$ is an 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.

IONIS-AGT-L$_{Rx}$ – IONIS-AGT-L$_{Rx}$ is a 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 75 million adults in the U.S. have hypertension, half of whom have uncontrolled hypertension. About 12-15 percent of patients with uncontrolled hypertension 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 are evaluating IONIS-AGT-L$_{RX}$ in a double-blinded, randomized, placebo-controlled, Phase 2 study in people with mild hypertension and in a second Phase 2 study in patients with TRH.

IONIS-AZ4-2.5-L$_{Rx}$ – IONIS-AZ4-2.5-L$_{Rx}$ is a Generation 2.5 LICA antisense medicine we designed to treat patients with CVD. We and AstraZeneca are collaborating to develop IONIS-AZ4-2.5-L$_{Rx}$ to treat patients with CVD.

IONIS-FXI-L$_{Rx}$ – IONIS-FXI-L$_{Rx}$ is a 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 double-blinded, randomized, placebo-controlled study of the parent medicine, IONIS-FXI$_{Rx}$, in people with end-stage renal disease 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, double-blind, 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. In October 2019, Bayer opted to continue to develop and commercialize IONIS-FXI-L_{Rx} following positive clinical results. Bayer plans to advance IONIS-FXI-L_{Rx} into a Phase 2 clinical trial. Bayer is responsible for all IONIS-FXI-L_{Rx} development, regulatory and commercialization activities and costs.

ION839 – ION839 (formerly IONIS-AZ6-2.5-L_{Rx}) is a Generation 2.5 LICA antisense medicine we designed to inhibit an undisclosed target. We and AstraZeneca are collaborating to develop ION839 to treat patients with NASH.

In October 2019, we initiated a Phase 1 clinical study evaluating ION839 in healthy volunteers. The current study is a randomized, blinded, placebo-controlled study designed to assess the safety and tolerability of multiple doses of ION839.

Rare Disease Medicines in Development

We are discovering and developing antisense medicines to treat people with rare diseases who have limited or no treatment options. We believe our antisense technology could offer effective therapies for these people. According to the NIH there are approximately 7,000 rare diseases, many life-threatening or fatal. Unfortunately, people with many of these severe and rare diseases have few or no effective therapies available. Since most of these diseases are genetic or have a genetic component, parents often pass the disease to their children resulting in profound impacts through multiple generations. Due to the severe nature of these diseases and the lack of available treatments, there is often an opportunity for more flexible and efficient development paths to the market. For example, SPINRAZA received FDA approval within five years following the start of its first Phase 1 study.

IONIS' Rare Disease Clinical Pipeline

RARE					
MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
AKCEA-TTR-L_{Rx}	hATTR polyneuropathy	Akcea			
AKCEA-APOCIII-L_{Rx}	FCS	Akcea			
IONIS-GHR-L_{Rx}	Acromegaly	Ionis			
IONIS-PKK-L_{Rx}	Hereditary angioedema	Ionis			
IONIS-TMPRSS6-L_{Rx}	β-thalassemia	Ionis			
IONIS-ENAC-2.5$_{Rx}$	Cystic fibrosis	Ionis			
ION357	Retinitis pigmentosa	ProQR			

AKCEA-TTR-L_{Rx} – See the medicine description under "Our Phase 3 Medicines" section above.

AKCEA-APOCIII-L_{Rx} – See the medicine description under "Ionis' Cardiometabolic and Renal Disease Clinical Pipeline" section above.

IONIS-GHR-L_{Rx} – IONIS-GHR-L_{Rx} is a 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 and has anabolic effects in adults. Several different diseases result from abnormally low or high levels of IGF-1, or an inappropriate response to this hormone.

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 mortality. 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 to patients with acromegaly. Current treatments to block IGF-1 include surgical removal of the pituitary gland, which is 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, double-blind, 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 acromegaly patients. The study is a randomized, double-blind, placebo-controlled, multi-center study in acromegaly patients uncontrolled on select long-acting somatostatin receptor ligands.

IONIS-PKK-L_{Rx} – IONIS-PKK-L_{Rx} is a 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 HAE attacks. In patients with frequent or severe attacks, doctors may use prophylactic treatment approaches to prevent or reduce 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, double-blinded, placebo-controlled study designed to assess the clinical efficacy, safety and tolerability of IONIS-PKK-L_{Rx} administered subcutaneously.

IONIS-TMPRSS6-L_{Rx} – IONIS-TMPRSS6-L_{Rx} is a 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 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 NTDT, including β-thalassemia intermedia. Although transfusions are not needed to support life in patients with NTDT, 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 December 2018, we presented positive Phase 1 data at the ASH Annual Meeting. In a randomized, double-blind, 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.

We are planning to begin a Phase 2 study of IONIS-TMPRSS6-L_{Rx} in 2020 in patients with NTDT β-thalassemia.

IONIS-ENAC-2.5_{Rx} – IONIS-ENAC-2.5_{Rx} is a Generation 2.5 antisense medicine we designed to selectively reduce epithelial sodium channel, or ENaC, to treat people with cystic fibrosis, or CF. 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 due to various 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 transgenic rodents, 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 CF in the animal model.

In December 2018, we initiated a Phase 1/2 double-blinded, placebo-controlled, dose-escalation study to evaluate the safety and efficacy of IONIS-ENAC-2.5_{Rx}. The study consists 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.

ION357 – ION357 (formerly IONIS-RHO-2.5$_{Rx}$), is a Generation 2.5 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 when rod photoreceptor function declines. 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.

Anti-Cancer and Other Medicines in Development

Cancer is an area of significant unmet medical need. Cancer is an extremely complex disease that involves a large number of targets. Using our antisense technology, we can validate multiple potential cancer targets for a variety of different cancers, and rapidly identify anti-cancer medicines. We preferentially select anti-cancer targets that can potentially provide a multi-faceted approach to treating cancer.

Our anti-cancer pipeline consists of antisense medicines that act upon biological targets associated with cancer progression, treatment resistance, and/or the tumor immune environment. Our alliances with AstraZeneca include an anti-cancer collaboration that expands our efforts. AstraZeneca brings significant experience that enables the identification of novel genetic and epigenetic targets for cancer. We also have collaboration agreements with University of Texas MD Anderson Cancer Center and Oregon Health and Science University Knight Cancer Institute to identify cancer targets and create novel antisense medicines to treat cancer.

In addition to oncology programs, we continue to advance other medicines in development that are outside of our core therapeutic areas, including IONIS-FB-L$_{Rx}$ for complement-mediated diseases we and Roche are developing, and antiviral medicines IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ GSK is developing.

Our Generation 2.5 chemistry enhances the potency and effectiveness of our antisense medicines, and potentially allows us to extend the applicability of our technology to cancers that are difficult to treat. For instance, STAT3 is a protein known to be important in the formation of cancer, however, it has been difficult to approach with traditional drug modalities. Data from a Phase 1b/2 clinical study of danvatirsen in combination with durvalumab, AstraZeneca's programmed death ligand, or PD-L1, blocking antibody showed evidence of antitumor activity in people with advanced solid tumors and recurrent metastatic head and neck cancer.

IONIS' Oncology/Other Clinical Pipeline

ONCOLOGY AND OTHER					
MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
IONIS-AR-2.5$_{Rx}$	Prostate cancer	Ionis/Suzhou-Ribo*			
Danvatirsen	Cancer	AstraZeneca			
IONIS-HBV$_{Rx}$/HBV-L$_{Rx}$	Hepatitis B virus infection	GSK			
IONIS-FB-L$_{Rx}$	Complement mediated diseases	Roche			

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IONIS-AR-2.5$_{Rx}$ – IONIS-AR-2.5$_{Rx}$ is a Generation 2.5 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.

Danvatirsen– Danvatirsen (formerly IONIS-STAT3-2.5$_{Rx}$) is a Generation 2.5 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. Physicians believe that overactivity in STAT3 prevents cancer cell death and promotes tumor cell growth.

In October 2018, we and AstraZeneca announced data from a Phase 1/2 study of danvatirsen 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.

AstraZeneca is evaluating danvatirsen in a range of cancer types as part of a broader oncology partnership evaluating Generation 2.5 antisense therapies against undruggable targets either alone or in combination with immuno-oncology agents, including in non-small cell lung cancer, bladder cancer and head and neck cancer.

IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ – IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ are antisense medicines 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 studies with IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ 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 1 month, including two patients who achieved reductions in HBsAg and HBV DNA below levels of detection. In the Phase 2 study with IONIS-HBV-L$_{Rx}$, the medicine demonstrated efficacy similar to IONIS-HBV$_{Rx}$. In these studies, both IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ demonstrated favorable safety and tolerability profiles.

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

IONIS-FB-L$_{Rx}$ – IONIS-FB-L$_{Rx}$ is a 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.

IgAN is one of the most common causes of inflammation that impairs the filtering ability of kidneys worldwide and is an important cause of chronic kidney disease and renal failure. Also known as Berger’s disease, IgAN is characterized by immunodeposits 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 current study is a randomized, blinded, 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.

Preclinical Medicines in Development

The efficiency and broad applicability of our technology enables us to develop medicines for a broad range of diseases. On average, it takes approximately 1-2 years to complete the preclinical studies necessary to support clinical development. In 2019, we added 10 new medicines to our preclinical pipeline.

IONIS' Preclinical Pipeline

	MEDICINES	INDICATION	PARTNER
NEUROLOGICAL	ION716	Prion disease	Ionis
	ION581	Angelman syndrome	Biogen
	ION260	Neurological disease	Biogen
	ION283	Lafora disease	Ionis
	ION373	Alexander disease	Ionis
	ION464	Neurological disease	Biogen
	ION541	Neurological disease	Biogen
RARE	ION663	Pulmonary disease	Ionis
CARDIOMETABOLIC & RENAL	ION547	Cardiometabolic disease	Ionis
	ION904	Cardiometabolic disease	Ionis
	ION224	NASH	Ionis
	ION532	Kidney disease	AstraZeneca

	MEDICINES	INDICATION	PARTNER
CANCER	ION929	Cancer	Ionis / Suzhou-Ribo*
	ION537	Cancer	MD Anderson
	ION251	Multiple myeloma	Ionis
	ION674	Lymphomas	Ionis / Suzhou-Ribo*
	ION736	Cancer	AstraZeneca
OTHER	ION253	GI Autoimmune disease	Janssen

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Akcea Therapeutics: Our Majority Owned Affiliate Focused on Developing and Commercializing Medicines to Treat People with Serious and Rare Diseases

We formed Akcea Therapeutics and Akcea began operations in 2015. Akcea is focused on developing and commercializing medicines to treat people with serious and rare diseases. As of December 31, 2019, we owned approximately 76 percent of Akcea. Akcea is commercializing TEGSEDI and WAYLIVRA, medicines we discovered and developed using our proprietary antisense technology. Additionally, Akcea has a mature pipeline of four of our novel medicines, including AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx}, and AKCEA-TTR-L_{Rx}, with the potential to treat rare and common diseases. Akcea is co-developing these four medicines with us.

This report includes financial information for Akcea as a separate business segment. See Note 7, *Segment Information and Concentration of Business Risk*, in the Notes to the Consolidated Financial Statements for additional information.

TEGSEDI – See the medicine description under "Our Marketed Medicines" section above.

WAYLIVRA –See the medicine description under "Our Marketed Medicines" section above

AKCEA-APO(a)-L_{Rx} – See the medicine description under "Our Phase 3 Medicines" section above.

AKCEA-TTR-L_{Rx} – See the medicine description under "Our Phase 3 Medicines" section above.

AKCEA-ANGPTL3-L_{Rx} – See the medicine description under "Cardiometabolic and Renal Disease Pipeline" section above.

AKCEA-APOCIII-L_{Rx} – See the medicine description under "Cardiometabolic and Renal Disease Pipeline" section above.

Antisense Technology

Our antisense technology is an innovative platform for discovering first-in-class and/or best-in-class medicines for treating disease. We believe this technology represents an important advance in the way we treat disease. Unlike most other drug technologies that work by affecting existing proteins in the body, 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 to antisense technology.
- Precise specificity: we design antisense medicines to target a single RNA, which minimizes or eliminates the possibility our medicines will bind 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 relatively 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 to potentially treat a wide range of diseases in a number of different therapeutic areas from severe and rare diseases to diseases that affect large patient populations. We focus our efforts on diseases in which there is a large unmet medical need with limited or no current treatments or in diseases for which we believe our medicines have a competitive advantage over existing therapies.

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 deoxyribonucleic acid, or 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.

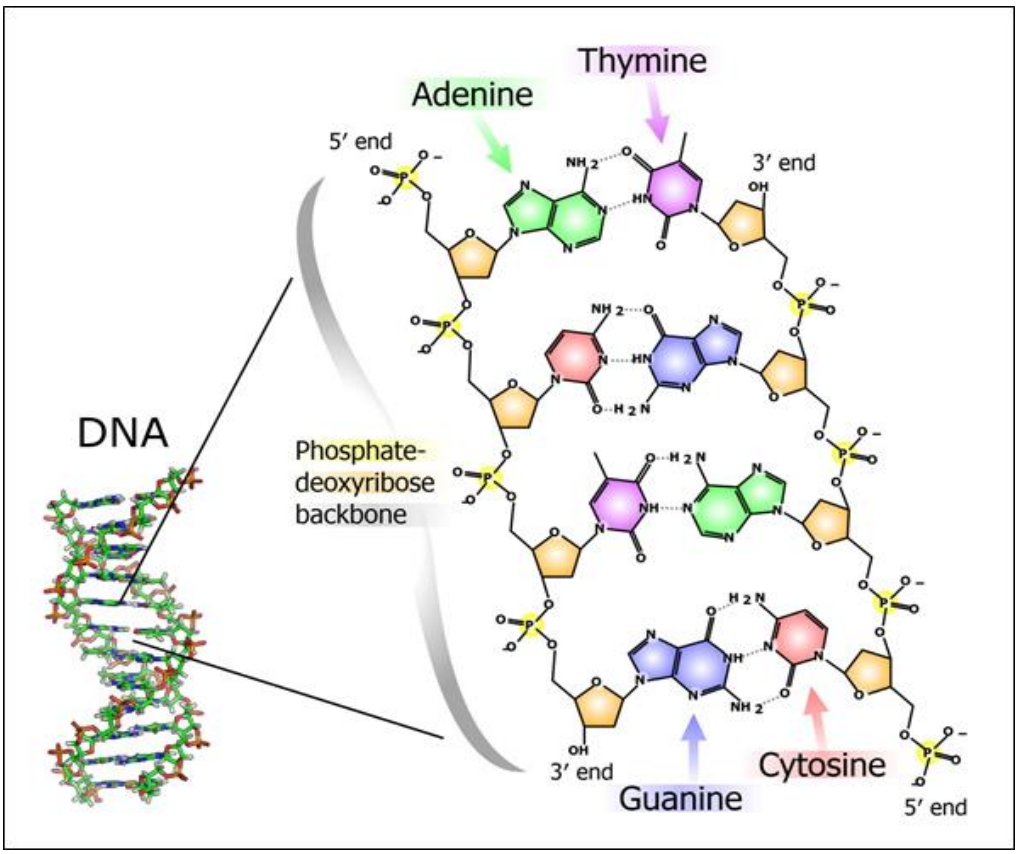


Figure 1: Illustration of DNA.

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.

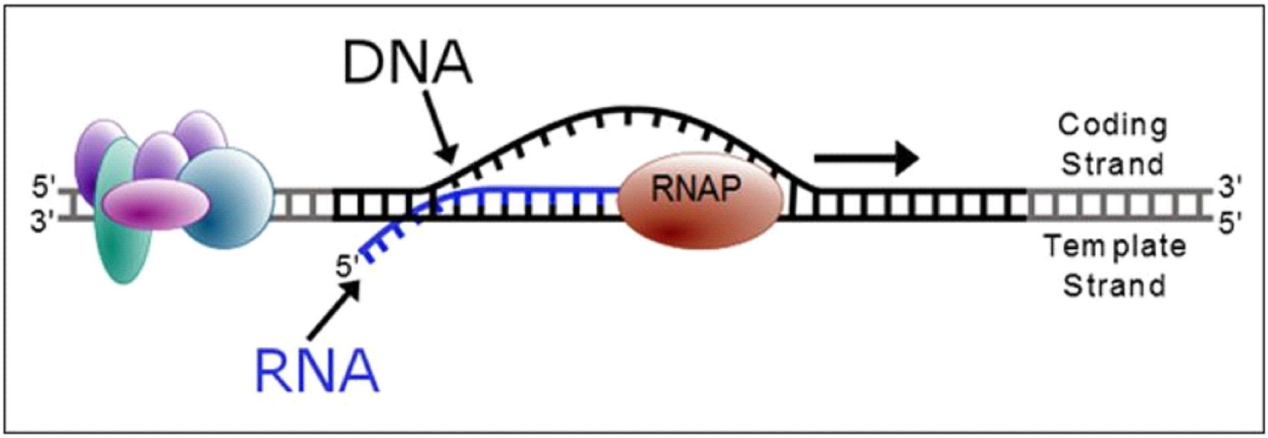


Figure 2: Transcription of information contained in a gene, or DNA, to RNA.

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).

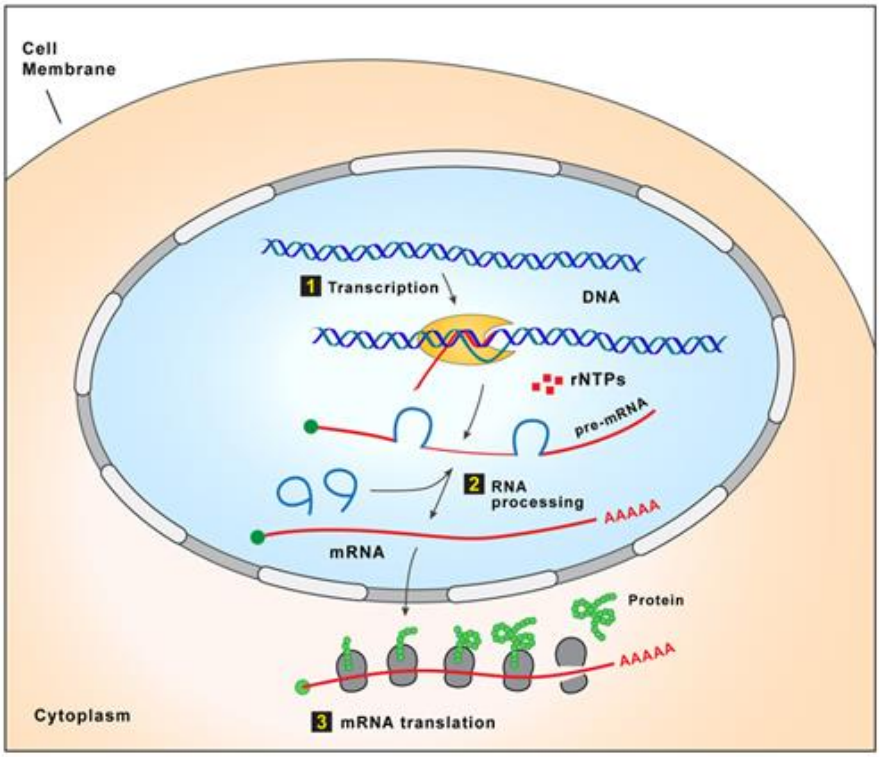


Figure 3: Translation of the protein-coding information contained in mRNA to protein.

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, this selectivity provides a level of specificity that is better than traditional medicines. As a result, 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 refer to our medicines that have passed these advanced screens as Generation 2+ medicines. 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 patient populations. Today several of our early stage medicines and those entering our pipeline use our most advanced antisense technology, including our next generation chemistries, Generation 2.5, and our LICA technology.

Generation 2.5 chemistry is an advancement that we have demonstrated increases the potency of our medicines by up to 10-fold over our Generation 2+ medicines. This increase in potency enables our medicines to engage targets in a broader array of tissues. We have published data demonstrating that our Generation 2.5 medicines generally have enhanced potency over our Generation 2+ medicines and are broadly distributed throughout the body to multiple tissues including liver, kidney, lung, muscle, adipose, adrenal gland, peripheral nerves and tumor tissues. Our Generation 2.5 medicines constitute some of our recently added new medicines 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 2019, we have an integrated assessment of data from multiple LICA medicines and over 1,100 subjects who have been treated with our LICA medicines. Our integrated assessment includes a substantial number of subjects on treatment for one year from randomized placebo-controlled dose-ranging studies. Our integrated assessment demonstrated that our LICA technology for liver targets can increase potency by up to 30-fold over our non-LICA antisense medicines.

In addition to the increase in potency, a favorable safety and tolerability profile was observed and was consistent across the LICA platform. For example, AKCEA-APO(a)-L_{Rx} 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). In the Phase 2 AKCEA-APO(a)-L_{Rx} study, AKCEA-APO(a)-L_{Rx} was the first and only medicine to selectively and robustly reduce Lp(a) levels below threshold levels associated with CVD in nearly all patients. This 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. The safety and tolerability profile from this study was favorable and there were no safety concerns related to platelets, liver or kidney function.

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 the pancreas, and initial results are promising.

Antisense Targets and Mechanisms

There are more than a dozen different antisense mechanisms that we can exploit 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, AKCEA-APO(a)-L_{Rx}, IONIS-FXI-$L_{Rx,}$, and others.

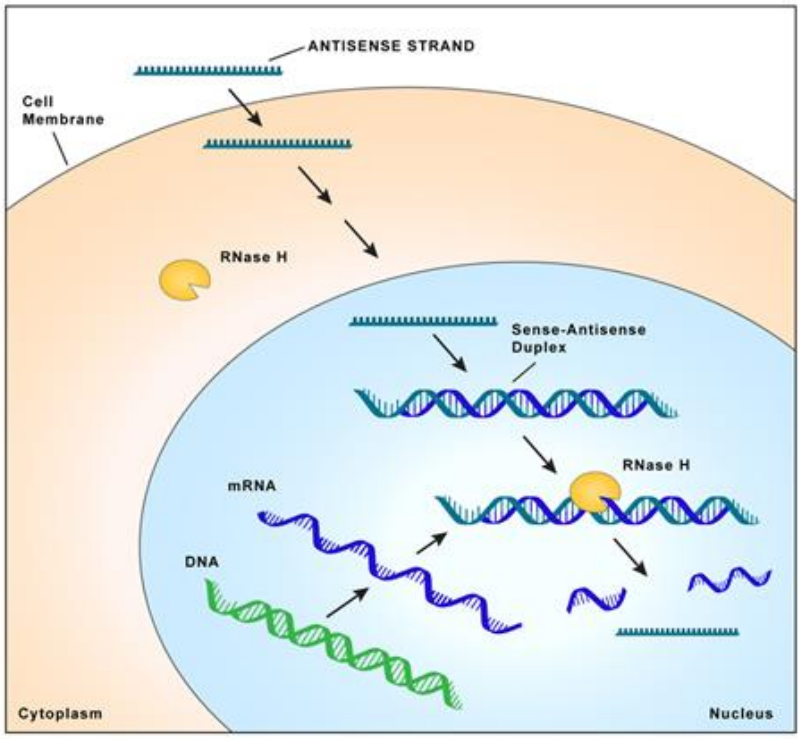


Figure 4: Antisense medicine using the RNase H mechanism of action.

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.

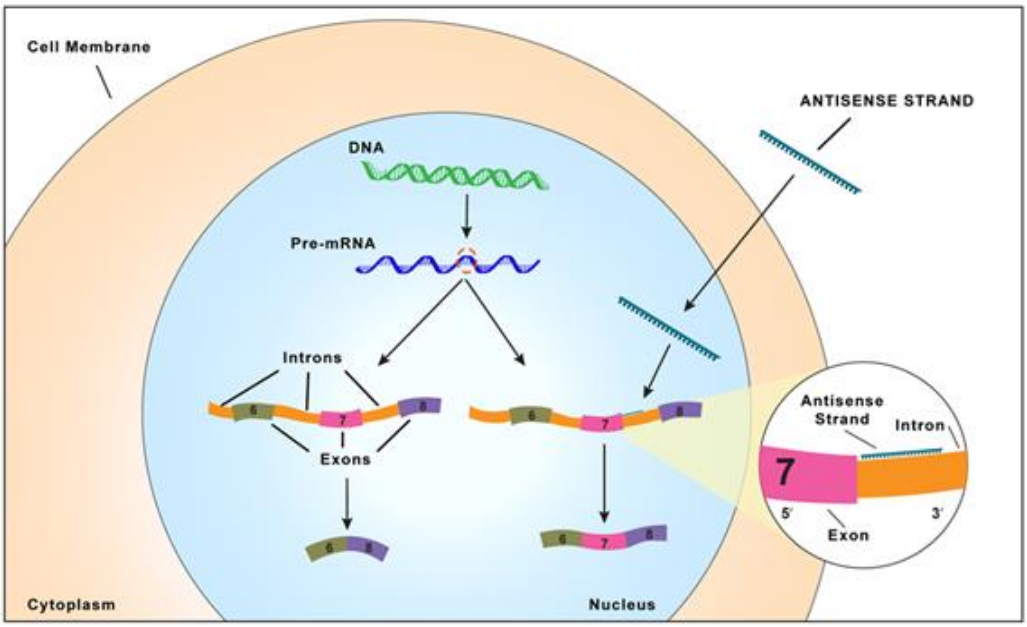


Figure 5: Antisense medicine altering splicing of the SMN2 mRNA.

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 various rare diseases, cardiometabolic diseases, neurologic diseases, cancer and other diseases.

Collaborative Arrangements

We strive to find the optimum organization to develop and commercialize each of our antisense medicines. We have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our medicines, advancing our technology, preparing to commercialize our medicines and selling our medicines. Our partners include the following companies, among others: AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis, Pfizer and Roche. Our partners bring resources and expertise that augment and build upon our internal capabilities and in many cases, add value by conducting development and regulatory activities and paying for these activities. The depth of our knowledge and expertise with antisense technology together with our strong financial position enables us to partner our medicines at what we believe is the optimal time to maximize the value of our medicines. We have distinct partnering strategies that we employ based on the specific program, therapeutic area and the expertise and resources our potential partners may bring to the collaboration.

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 2019, we recognized more than $1.1 billion in revenue, primarily from our partnerships. 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. In December 2017, we entered into a collaboration with Biogen to identify new antisense medicines for the treatment of SMA. We and Biogen are currently developing eight medicines under our collaborations, including medicines 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 February 2020, we have generated more than $2.5 billion from our Biogen collaborations, including $1 billion we received from Biogen in the second quarter of 2018 for our 2018 strategic neurology collaboration.

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. Biogen reported in January 2020 that SPINRAZA was approved in over 50 countries around the world. From inception through December 2019, we generated more than $1 billion in total revenue under our SPINRAZA collaboration, including more than $640 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 all further 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.

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 target. Biogen will have the option to license the selected target after it completes the IND-enabling toxicology study. If Biogen exercises its option to license a medicine, it will assume all further 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. Through December 2019, we have advanced six targets under this collaboration, including two new targets we advanced in the fourth quarter of 2019. We have generated over $1.05 billion in payments through February 2020, including $15 million we generated in the fourth quarter of 2019 for advancing two targets under this collaboration.

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 all further global development, regulatory and commercialization responsibilities and costs for that medicine. We are currently advancing five medicines in development under this collaboration, including a medicine for Parkinson's disease, two medicines for ALS and two medicines for undisclosed targets. In December 2018, Biogen exercised its option to license one of our ALS medicines, tofersen, and as a result Biogen is now responsible for all further 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 antisense medicines developed under this collaboration. We have generated over $240 million through February 2020, including $10 million we earned in the fourth quarter of 2019 when Biogen advanced IONIS-C9$_{Rx}$ in development.

2012 Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize up to three 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 ION581 for Angelman syndrome. If Biogen exercises its option to license a medicine, it will assume all further 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 all further 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 of any medicines resulting from each program under the agreement. We have generated over $130 million through February 2020, including $45 million we earned when Biogen licensed IONIS-MAPT$_{Rx}$ and $10 million when Biogen advanced ION581, both of which occurred in the fourth quarter of 2019. We also achieved a $7.5 million milestone payment in the first quarter of 2020 for advancing IONIS-MAPT$_{Rx}$.

Research, Development and Commercialization Partners

AstraZeneca

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 three medicines from us: IONIS-AZ4-2.5-L$_{Rx}$, a medicine we designed to treat cardiovascular disease and our first medicine that combines our Generation 2.5 and LICA technology, ION532, a medicine we designed to treat a genetically associated form of kidney disease and ION839, a medicine we designed to inhibit an undisclosed to treat patients with NASH. AstraZeneca is responsible for all further 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 $4 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. We have generated over $175 million in payments through February 2020, including a $10 million milestone payment we earned in the fourth quarter of 2019 when AstraZeneca initiated a Phase 1 trial for ION839.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense medicines to treat cancer. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize danvatirsen for the treatment of cancer. AstraZeneca is responsible for all global development, regulatory and commercialization activities for danvatirsen. We and AstraZeneca have evaluated danvatirsen in people with head and neck cancer, advanced lymphoma and advanced metastatic hepatocellular carcinoma. AstraZeneca is evaluating danvatirsen in combination with durvalumab, AstraZeneca's PD-L1, blocking medicine, in people with head and neck cancer, metastatic bladder cancer and metastatic non-small cell lung 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 all further global development, regulatory and commercialization activities and costs for such medicine. In the fourth quarter of 2018, we added a second medicine under our oncology collaboration, ION736, (formerly IONIS-AZ7-2.5$_{Rx}$) to our preclinical pipeline,.

Under the terms of this agreement, we received $31 million in upfront payments. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. If AstraZeneca successfully develops danvatirsen and ION736 under the research program, we could receive license fees and milestone payments of up to more than $450 million. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any medicines resulting from these programs. We have generated over $125 million in payments through February 2020, including nearly $30 million in milestone payments we achieved when AstraZeneca advanced danvatirsen and ION736 in the fourth quarter of 2018.

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 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. We have generated over $185 million through February 2020, including a $10 million milestone payment we earned in the fourth quarter of 2019 when Bayer decided it would advance IONIS-FXI-L$_{Rx}$.

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 rare and serious diseases, including infectious diseases and some conditions causing blindness. Under the collaboration, we received upfront payments of $35 million. Our collaboration with GSK includes two medicines targeting hepatitis B virus, or HBV: IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$, 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. We have generated over $185 million in payments through February 2020, including a $25 million license fee we earned in the third quarter of 2019 when GSK licensed the HBV program.

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. Janssen had the option to license medicines from us through the designation of development candidates for up to three programs. Under our collaboration, Janssen licensed ION253 in November 2017, which is currently in preclinical development. Prior to Janssen's license of ION253, we were responsible for the discovery activities to identify development candidates. Under the license, Janssen is responsible for the global development, regulatory and commercial activities 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 medicines resulting from this collaboration. We are eligible to receive up to $285 million in milestone payments and license fees for ION253. We have generated over $75 million through February 2020.

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 antisense 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. We have generated over $145 million through February 2020, including $35 million in milestone payments we generated in the first quarter of 2019 when Roche dosed the first patient in a Phase 3 study for 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 all further 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.

Akcea Collaborations

The following collaboration agreements relate to Akcea, our majority owned affiliate. Our consolidated results include all the revenue earned, cash received and expenses incurred under these collaboration agreements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on the statement of operations and a separate line within stockholders' equity on our consolidated balance sheet.

Novartis

In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Akcea received a $75 million upfront payment in the first quarter of 2017. In February 2019, Novartis licensed AKCEA-APO(a)-L_{Rx} and we earned a $150 million license fee. Novartis is responsible for conducting and funding all future development, regulatory and commercialization activities for AKCEA-APO(a)-L_{Rx}, including a global Phase 3 cardiovascular outcomes study, which Novartis initiated in December 2019. In connection with Novartis' license of AKCEA-APO(a)-L_{Rx}, Akcea and Novartis established a more definitive framework under which the companies would negotiate the co-commercialization of AKCEA-APO(a)-L_{Rx} in selected markets. Included in this framework is an option by which Novartis could solely commercialize AKCEA-APO(a)-L_{Rx} in exchange for Novartis paying Akcea increased commercial milestone payments based on sales of AKCEA-APO(a)-L_{Rx}. When Novartis decided to not exercise its option for AKCEA-APOCIII-L_{Rx}, Akcea retained rights to develop and commercial AKCEA-APOCIII-L_{Rx}.

Under the collaboration, Akcea is eligible to receive up to $675 million in milestone payments related to AKCEA-APO(a)-L_{Rx}. Akcea is also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of AKCEA-APO(a)-L_{Rx}. We have generated approximately $345 million through February 2020 under this collaboration. Akcea paid us a portion of the upfront payment it received from Novartis in 2017 and 50 percent of the license fee it received from Novartis in 2019 and will pay 50 percent of milestone payments and royalties to us as sublicense fees.

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 the IPO in July 2017.

Pfizer

In October 2019, Akcea initiated a collaboration with Pfizer for the license of AKCEA-ANGPTL3-L_{Rx} to treat people with cardiovascular and metabolic diseases. Akcea conducted a Phase 2 study of AKCEA-ANGPTL3-L_{Rx} for the treatment of non-alcoholic fatty liver disease, or NAFLD. Pfizer is responsible for all development and regulatory activities and costs beyond those associated with this recently completed Phase 2 study.

Under the terms of the agreement, Akcea received a $250 million upfront license fee. Akcea is 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. Akcea has retained the rights to co-commercialize AKCEA-ANGPTL3-L_{Rx} in the U.S. and certain additional markets. The license fee, milestone payments and royalties will be split equally between us and Akcea. During the fourth quarter of 2019, we received 6.9 million shares of Akcea common stock for payment of the $125 million sublicense fee Akcea owed us.

PTC Therapeutics

In August 2018, Akcea entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America. Under the license agreement, Akcea is eligible to receive up to $26 million in payments. Akcea is 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 Akcea 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. Consistent with the agreements between Ionis and Akcea, the companies will share all payments, including royalties. We have generated over $20 million through February 2020, including $6 million when WAYLIVRA was approved in the EU in the second quarter of 2019 and $4 million when PTC received approval for TEGSEDI in Brazil in the fourth quarter of 2019.

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 also have the potential to earn a portion of payments that Alnylam receives from licenses of our technology it grants to its partners, plus royalties. 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.

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 have internal capabilities to manufacture our 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 many other oligonucleotide 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 the 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 28,700 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 an initial term ending in June 2021 with an option to extend the lease for up to two additional five-year periods. 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, would not 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, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx}:

SPINRAZA

Pursuant to our collaboration with Biogen, Biogen is responsible for SPINRAZA drug supply. We provided Biogen with API for SPINRAZA in 2018 under our manufacturing agreement with Biogen, which ended in September 2018. Biogen has an oligonucleotide synthesis manufacturing facility that gives it the capability to manufacture SPINRAZA.

TEGSEDI

For TEGSEDI's commercial drug supply, Akcea is using CMOs to produce custom raw materials, API and finished goods. Akcea's CMO partners have extensive technical expertise and cGMP experience. We believe Akcea's current network of CMO partners are capable of providing sufficient quantities to meet anticipated commercial demands.

WAYLIVRA

We have supplied the API and the finished drug product for WAYLIVRA's commercial launch. We believe Akcea has sufficient API and drug product for at least the first two years of WAYLIVRA's commercial launch. Akcea plans to leverage its relationships with CMOs to procure its own long-term raw material and drug supplies at competitive prices in the future.

Tominersen

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

Tofersen

Pursuant to our collaboration with Biogen, Biogen is responsible for tofersen drug supply. 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. 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.

AKCEA-APO(a)-L_{Rx}

We have supplied the API and the finished drug product for AKCEA-APO(a)-L_{Rx} which Akcea sold to Novartis to use in its Phase 3 study. Pursuant to our collaboration with Novartis, Novartis is responsible for any further AKCEA-APO(a)-L_{Rx} drug supply.

AKCEA-TTR-L_{Rx}

We have supplied the API and the finished drug product for AKCEA-TTR-L_{Rx} that we believe will be sufficient through the completion of the Phase 3 program for AKCEA-TTR-L_{Rx}. Akcea plans to leverage its relationships with CMOs to procure its own long-term raw material and drug supplies at competitive prices in the future.

LICA Medicines

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

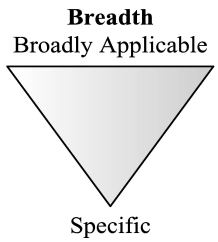
Patents and Proprietary Rights

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.

Type of Patent Claim
(Broadly Applicable to Specific)

- Chemically Modified Nucleosides and Oligonucleotides (target and sequence independent)
- Antisense Drug Design Motifs (target and sequence independent)
- Therapeutic Methods (sequence and chemistry independent)
- Antisense Sequence (chemistry independent)
- Drug Composition



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):

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

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, 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 pursued patent claims to antisense drug design motifs incorporating bicyclic nucleoside analogs, which include both locked nucleic acids, or "LNA" and cEt. In Europe, we have been granted claims drawn to certain short gapmer oligonucleotides with bicyclic nucleosides, which include locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders. 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:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	7,015,315	GAPPED OLIGONUCLEOTIDES	2023	2’-O-alkyl-O-alkyl gapmer oligonucleotides.
Europe	2021472	COMPOUNDS AND METHODS FOR MODULATING GENE EXPRESSION	2027	Short gapmer oligonucleotides, having wings of 2 bicyclic nucleosides, and a gap of 10 deoxynucleotides for the treatment of cardiovascular or metabolic disorders
United States	7,750,131	5’-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	5’-Methyl BNA containing gapmer compounds
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	2092065	ANTISENSE COMPOUNDS	2027	Gapmer compounds having 2’-modifed and LNA nucleosides
Europe	2410053	ANTISENSE COMPOUNDS	2027	Gapmer compounds having wings comprised of 2’-MOE and bicyclic nucleosides
Europe	2410054	ANTISENSE COMPOUNDS	2027	Gapmer compounds having a 2’-modifed 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
Europe	3067421	OLIGOMERIC COMPOUNDS COMPRISING BICYCLIC NUCLEOTIDES AND USES THEREOF	2032	Gapmer oligonucleotides having at least one bicyclic, one 2’-modified nucleoside and on 2’-deoxynucleoside

LIgand-Conjugated Antisense (LICA) Technology

We have also pursued 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:

Jurisdiction	Patent	Title	Expiration	Description of Claims
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 product’s 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 European:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	8,361,977	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2030	Sequence and chemistry (full 2'-MOE) of SPINRAZA
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	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
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	Antisense compounds including SPINRAZA for treating SMA

TEGSEDI and Transthyretin

We obtained issued claims covering TEGSEDI in the U.S. and Europe. We believe the issued U.S. claims protect TEGSEDI from generic competition in the U.S. and Europe until at least 2031. We are also pursuing additional patent applications designed to protect TEGSEDI in other foreign jurisdictions. The table below lists some key issued patents protecting TEGSEDI in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
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 an issued patent claiming the specific sequence and chemical composition of WAYLIVRA in the U.S. and Europe. We believe the issued U.S. and Europe 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:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
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 CIII (APOCIII) EXPRESSION	2032	Methods of using APOCIII antisense oligonucleotides for reducing pancreatitis and chylomicronemia and increasing HDL

Tominersen and Huntingtin

We obtained issued claims covering tominersen in the U.S. and Europe. We believe the issued U.S. and Europe claims protect tominersen from generic competition in the U.S. until at least 2030. We are also pursuing additional patent applications designed to protect tominersen in foreign jurisdictions. The table below lists some key issued patents protecting tominersen in U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
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
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

Tofersen and SOD-1

We believe tofersen is protected from generic competition in the U.S. until at least 2036. Additional patent protection designed to protect tofersen is being pursued in foreign jurisdictions. 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	10,385,341	COMPOSITIONS FOR MODULATING SOD-1 EXPRESSION	2036	Composition of tofersen
United States	8,993,529	ANTISENSE MODULATION OF SUPEROXIDE DISMUTASE 1, SOLUBLE EXPRESSION	2021	Antisense compound specifically hybridizable within nucleotide region of SOD-1 targeted by tofersen
Europe	EP2270024	ANTISENSE MODULATION OF SUPEROXIDE DISMUTASE 1, SOLUBLE EXPRESSION	2022	Antisense compound specifically hybridizable within nucleotide region of SOD-1 targeted by tofersen

AKCEA-APO(a)-L_{Rx}

We believe AKCEA-APO(a)-L_{Rx} is protected from generic competition in the U.S. until at least 2034. In addition, if AKCEA-APO(a)-L_{Rx} is approved by the FDA, we will seek patent term extension to recapture a portion of the term lost during FDA regulatory review, extending the term of this patent beyond 2034. We are pursuing additional patent applications designed to protect AKCEA-APO(a)-L_{Rx} worldwide. The table below lists some key issued patents protecting AKCEA-APO(a)-L_{Rx} in the U.S.:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	9,574,193	METHODS AND COMPOSITIONS FOR MODULATING APOLIPOPROTEIN (A) EXPRESSION	2033	Compounds that include an oligonucleotide complementary to the region of the Apo(a) transcript where AKCEA-APO(a)-L_{Rx} binds
United States	10,478,448	METHODS AND COMPOSITIONS FOR MODULATING APOLIPOPROTEIN (A) EXPRESSION	2033	Methods of treating hyberlipidemia using oligonucleotide complementary to the region of the Apo(a) transcript where AKCEA-APO(a)-L_{Rx} binds
United States	9,181,550	COMPOSITIONS AND METHODS FOR MODULATING APOLIPOPROTEIN (a) EXPRESSION	2034	The composition of AKCEA-APO(a)-L_{Rx}

AKCEA-TTR-L_{Rx} and Transthyretin

We are pursuing claims covering AKCEA-TTR-L_{Rx} in the U.S. We believe the claims when granted will protect AKCEA-TTR-L_{Rx} from generic competition in the U.S. until at least 2034. We are also pursuing additional patent applications to protect AKCEA-TTR-L_{Rx} in foreign jurisdictions.

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.

Numerous regulatory authorities in addition to the FDA, including, in the U.S., the Centers for Medicare & 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. Only those claims relating to safety and efficacy that the FDA has approved may be used in labeling. We are only allowed to use promotional communications regarding a drug that are consistent with the information in the drug's approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses.

For any approved medicine, domestic and foreign sales of the medicine depend, in part, on the availability and amount of reimbursement by third party payors, including governments and private health plans. Private health plans may seek to manage cost and use of our medicines by implementing coverage and reimbursement limitations. 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, including Akcea, and that of our commercial partners to successfully commercialize approved medicines.

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.

Other healthcare laws that may affect our ability to operate include 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;
- 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 and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members.

Our operations may be directly, or indirectly through our customers, distributors, or other business partners, subject to various federal and state fraud and abuse laws, including, without limitation, anti-kickback statutes and false claims statutes. These laws may impact, among other things, our, Akcea's, and our partners' proposed sales, marketing and education programs.

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 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 AKCEA-APO(a)-L_{Rx}.

SPINRAZA

We consider the following medicines as competitors and potential future competitors to SPINRAZA:

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]	Next Milestones [1]
Zolgensma (AVXS-101)	Novartis	Gene therapy designed to target the genetic root cause of SMA by replacing the function of the missing or nonworking SMN1 gene	Approved (U.S.)	Infusion	- Approval decision for EU expected in the first quarter of 2020 - Approval decision for Japan expected in the first half of 2020
Risdiplam (RG7916)	PTC Therapeutics/ Roche/ SMA Foundation	A small molecule medicine that modulates splicing of the SMN2 gene	NDA Submitted	Oral	Prescription Drug User Fee Act, or PDUFA, date set for May 2020

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

In May 2019, Zolgensma was approved for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy including those who are presymptomatic at diagnosis, becoming the first approved medicine to compete with SPINRAZA. In November 2019, the FDA accepted Roche and PTC's NDA and granted priority review for risdiplam. The filing submission includes 12-month data from pivotal FIREFISH and SUNFISH trials in a broad population of people living with Type 1, 2, or 3 SMA.

TEGSEDI and AKCEA-TTR-L_{Rx}

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

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]	Next Milestones [1]
Onpattro	Alnylam	An RNAi medicine formulated with lipid nanoparticles to inhibit TTR mRNA	Approved (hATTR)/ Phase 3 (ATTR)	Intravenous infusion with pre-treatment with steroids	Topline data for the APOLLO-B (Phase 3 study) is expected in 2021
Vyndaqel & Vyndamax (Tafamidis)	Pfizer	A small molecule medicine to stabilize TTR protein	Commercially available in the U.S. for cardiomyopathy and in the EU for stage 1 polyneuropathy and cardiomyopathy	Oral	None reported
Vutrisiran	Alnylam	An RNAi medicine conjugated with GalNAC to inhibit TTR mRNA	3	Subcutaneous Injections	Topline data expected for HELIOS-A (Phase 3) study in 2021
AG10	Eidos	Small molecule that binds and stabilizes TTR in the blood	1	Oral	Phase 3 study planned to begin in the first quarter of 2020

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

Our main competition for Tegsedi is Onpattro (patisiran), marketed by Alnylam Pharmaceuticals. Although ONPATTRO requires intravenous administration by a healthcare provider in a clinical setting 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 Onpattro and vutrisiran could compete directly against AKCEA-TTR-L_{Rx}, given their transthyretin-silencing profile. Vyndaqel and Vyndamax, marketed by Pfizer, were approved in the U.S. and in the EU. They are two oral formulations of the transthyretin stabilizer, and currently the only medicines approved by the FDA to treat ATTR-CM.

WAYLIVRA

We believe that the following medicines could compete with WAYLIVRA:

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]	Next Milestones [1]
Gemcabene	NeuroBo Pharmaceuticals	Monocalcium salt of a dialkyl ether dicarboxylic acid	2	Oral	Currently on partial clinical hold, which was issued by the FDA in 2004
Myalept (metreleptin)	Amryt Pharma	Leptin replacement therapy	2	Subcutaneous Injections	None reported
ARO-APOC3	Arrowhead Pharmaceuticals	Targets APOCIII by utilizing Targeted RNAi Molecule Platform	1	Subcutaneous Injections	Plans to initiate pivotal (Phase 3) study in 2020

(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:

C	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]	Next Milestones [1]
WVE-120101/ WVE-120102	Wave Life Sciences	Antisense medicines targeting mHTT SNP-1 and SNP-2	1b/2a	Intrathecal Infusion	Topline data from PRECISION-HD1 is expected in the second half of 2020
Selisistat	AOP Orphan	An orally active, selective SIRT1 inhibitor	2	Oral	None reported
VX15	Vaccinex	A monoclonal antibody that blocks the activity of SEMA4D	2	Intravenous Infusion	Phase 2 (SIGNAL) topline data is anticipated in second half of 2020

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

Tofersen

We believe that the following medicine could compete with tofersen:

C	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]	Next Milestones [1]
Arimoclomol	Orphazyme	Provides cellular protection from abnormal proteins by activating molecular "chaperone" proteins that can repair or degrade the damaged proteins	3	Oral	Results of the Phase 3 trial in ALS are expected in the first half of 2021

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

Employees

As of February 20, 2020, we employed 817 people, including 294 Akcea employees. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees, and management considers relations with our employees to be good.

Information about our Executive Officers

The following sets forth certain information regarding our executive officers as of February 20, 2020:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	74	Executive Chairman of the Board of Directors
Brett P. Monia, Ph.D.	58	Chief Executive Officer
C. Frank Bennett, Ph.D.	63	Chief Scientific Officer
Onaiza Cadoret-Manier	55	Chief Corporate Development and Commercial Officer
Richard S. Geary, Ph.D.	62	Senior Vice President, Development
Elizabeth L. Hougen	58	Senior Vice President, Finance and Chief Financial Officer
Patrick R. O'Neil, Esq.	46	Senior Vice President, Legal, General Counsel, Chief Compliance Officer and Corporate Secretary
Eric E. Swayze, Ph.D.	54	Senior Vice President, Research

Management Transitions

In January 2020, Dr. Crooke, our founder and Chief Executive Officer, transitioned from Chief Executive Officer to Executive Chairman of our Board of Directors. As Executive Chairman, Dr. Crooke is responsible for the activities of the board and will remain active in the company, providing strategic advice and continuing to participate in the scientific activities. Dr. Monia, who was our Chief Operating Officer and a member of our team since our founding over 30 years ago, began serving as our Chief Executive Officer in January 2020.

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.

BRETT P. MONIA, Ph.D.

Chief Executive Officer

Dr. Monia was promoted to Chief Executive Officer in January 2020. From January 2019 to December 2019, Dr. Monia served as Chief Operating Officer. From January 2012 to January 2019, 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.

Chief Scientific Officer

Dr. Bennett was promoted to Chief Scientific Officer in January 2020. 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

Chief Corporate Development and Commercial Officer

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.

Senior Vice President, Development

Dr. Geary has served as Ionis' Senior Vice President, Development since August 2008. 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

Senior Vice President, Finance and Chief Financial Officer

Ms. Hougen has served as Ionis' Senior Vice President, Finance and Chief Financial Officer since January 2013. 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.

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

Mr. O'Neil has served as Ionis' Senior Vice President, Legal and General Counsel since January 2013. Mr. O'Neil also serves as our Chief Compliance Officer and Corporate Secretary. 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.

ERIC E. SWAYZE, Ph.D.

Senior Vice President, Research

Dr. Swayze was promoted to Senior Vice President of Research at Ionis Pharmaceuticals in January 2020. He is responsible for leading preclinical antisense drug discovery and antisense technology 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 Associated with our Ionis Core and Akcea Therapeutics Businesses

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 payors 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 payors 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 payors 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 payors.

Based on the profile of our medicines, physicians, patients, patient advocates, payors 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 ONPATTRO (patisiran), marketed by Alnylam Pharmaceuticals, Inc. Although ONPATTRO 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 and Akcea 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, 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 engage 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 payors 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. Marketing and sales capability is another factor relevant to the competitive position of our medicines, and we will primarily rely on our partners and Akcea to provide this capability.

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

- ZOLGENSMA (approved in the U.S. for the treatment of pediatric patients less than two years of age with SMA) and risdiplam (RG7916) could compete with SPINRAZA;
- ONPATTRO (approved in the U.S., Europe and Brazil for a similar indication as TEGSEDI), VYNDAQEL and VYNDAMAX (approved in the U.S. for patients with both hereditary and wild type ATTR cardiomyopathy and in the EU for stage 1 hATTR amyloidosis with polyneuropathy and cardiomyopathy), AG10 and vutrisiran could compete with TEGSEDI;
- ARO-APOC3, Myalept and gemcabene could compete with WAYLIVRA;
- WVE-120101/WVE-120102, Selistat and VX15 could compete with tominersen;
- Arimoclomol could compete with tofersen; and
- ONPATTRO, VYNDAQEL and VYNDAMAX, vutrisiran and AG10 could complete with AKCEA-TTR-$L_{Rx;}$.

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 AKCEA-APOCIII-L_{Rx} and TEGSEDI inhibits the production of the same protein as AKCEA-TTR-L_{Rx}. We believe the enhancements we incorporated into AKCEA-APOCIII-L_{Rx} and AKCEA-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 AKCEA-APOCIII-L_{Rx} or AKCEA-TTR-L_{Rx} instead of WAYLIVRA or TEGSEDI, respectively, it will reduce the revenue we derive from those medicines. In addition, while AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx} and WAYLIVRA use different mechanisms of action, if AKCEA-ANGPTL3-L_{Rx} can effectively lower triglyceride levels in FCS patients, it may likewise reduce the revenue we derive from WAYLIVRA and AKCEA-APOCIII-L_{Rx}.

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 Risk Evaluation and Mitigation Strategy, or 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, 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, 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 Akcea 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, Akcea must effectively manage its marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. Akcea may not be successful in doing so. To commercialize WAYLIVRA in the initial indications Akcea is planning to pursue and to continue the commercialization of TEGSEDI, Akcea will need to optimize and maintain specialty sales forces in the global regions where it currently markets or expects 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 Akcea's management team and other employees have experience commercializing medicines, as a company Akcea has limited experience marketing, selling and distributing medicines, and there are significant risks involved in building, tailoring, optimizing and managing a commercial infrastructure. Beginning in September 2019, Akcea announced several changes to its senior leadership team, including the departure of its Chief Executive Officer, its President, and its Chief Operating Officer and the recent resignation of its Chief Financial Officer, whose resignation is to become effective on April 1, 2020, and the appointment of an interim Chief Executive Officer, a new Chief Commercial Officer and a new Chief Operating Officer. The effectiveness of the senior leadership team following these transitions, new leaders as they fill in these roles, and any further transition as a result of these changes could impair Akcea's ability to manage its business.

It is expensive and time consuming for Akcea to maintain its own sales forces and related compliance protocols to market TEGSEDI and WAYLIVRA, and it will be increasingly expensive and time consuming when Akcea commercially launches additional medicines, if approved. Akcea may never successfully optimize or manage this capability and any failure could harm the commercial launch of WAYLIVRA or adversely affect TEGSEDI sales. Additionally, Akcea and its partners, if any, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel. As a result of Akcea's receipt of a CRL from the FDA regarding the new drug application for WAYLIVRA, on September 6, 2018, Akcea enacted a plan to reorganize its workforce to better align with the immediate needs of the business. In connection with this reorganization plan, Akcea reduced its workforce by approximately 12% and will need to increase its operations and expand its use of third -party contractors if WAYLIVRA is approved in the United States.

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

To the extent we and Akcea decide to rely on third parties to commercialize TEGSEDI or WAYLIVRA in a particular geographic market, we may receive less revenue than if Akcea commercialized TEGSEDI or WAYLIVRA by itself. For example, in August 2018, Akcea granted PTC Therapeutics International Limited, or PTC Therapeutics, the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries, and Akcea will continue to rely on PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in those geographic markets. In addition, in August 2018 Akcea entered into an agreement with Accredo Health Group, Inc., or Accredo, a subsidiary of Express Scripts, to be Akcea's specialty pharmacy partner for distribution of TEGSEDI in the U.S. Further, Akcea has less control over the sales efforts of other third parties, including PTC Therapeutics and Accredo, involved in commercializing TEGSEDI or WAYLIVRA.

If Akcea cannot effectively build and manage its 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.

If government or other third-party payors 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 payors. 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 United States 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 payors. These studies might require us to commit a significant amount of management time and financial and other resources. Third-party payors 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 payors, 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 payors. Therefore, coverage and reimbursement for medicines can differ significantly from payor to payor. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the PPACA, 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 by the Trump administration 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. It is unclear how this decision, future decisions, subsequent appeals, and other efforts to repeal and replace the Affordable Care Act 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 United States and in international markets. For example, in the United States, 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. At the federal level, the Trump administration's budget proposal for fiscal year 2020 contains further drug price control measures that could be enacted during the budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain medicines under Medicare Part B, to allow some states to negotiate prices under Medicaid, and to eliminate cost sharing for generic medicines for low-income patients. Further, the Trump administration released a "Blueprint" to lower medicine prices and reduce out of pocket costs of medicines that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of medicines paid by consumers. The Department of Health and Human Services has solicited feedback on some of these measures and, at the same time, has implemented others under its existing authority. While some of these and other measures may require additional authorization to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and administrative measures to control drug costs. 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 United States or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

If Biogen cannot manufacture finished drug product for SPINRAZA or the post-launch supply of the active drug substance for SPINRAZA, SPINRAZA may not maintain commercial success.

Biogen is responsible for the long-term supply of both SPINRAZA drug substance and finished drug product. Biogen may not be able to reliably manufacture SPINRAZA drug substance and drug product to support the long-term commercialization of SPINRAZA. If Biogen cannot reliably manufacture SPINRAZA drug substance and drug product, SPINRAZA may not maintain commercial success, which will harm our ability to generate revenue.

If we or our partners fail to obtain regulatory approval for our medicines and additional approvals for SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, 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 Akcea received a CRL from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in Akcea's clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. Akcea also received a Non-W from Health Canada for WAYLIVRA in November 2018. We and Akcea 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 United States;
- 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 the manufacturing processes or facilities of third-party manufacturers who manufacture clinical and commercial supplies for our medicines; 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, and our medicines in development, 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, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx}. If any of our medicines in clinical studies, including tominersen, tofersen, AKCEA-APO(a)-$L_{Rx,}$ and AKCEA-TTR-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, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-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.

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 Akcea to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. Akcea has 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 both WAYLIVRA and TEGSEDI. Adverse events or results from these studies or the EAPs could negatively impact Akcea's 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, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx}, could reduce the commercial potential or viability of our medicines.

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 or our partner would need to optimize and manage large-scale commercial manufacturing capabilities either on our own or through a third-party manufacturer. We and Akcea will rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and WAYLIVRA. 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 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 current Good Manufacturing Practices 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 Good Manufacturing Practices, 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.

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, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-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 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 SPINRAZA, TEGSEDI and WAYLIVRA.

Risks Associated with our Businesses as a Whole

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, 2019, we had an accumulated deficit of approximately $0.7 billion and stockholders' equity of approximately $1.7 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 research grants and 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.

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, federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating losses is limited. It is uncertain if and to what extent various states will conform to the federal Tax Act.

In addition, under Section 382 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.

Since corporate partnering is a significant part of our strategy to fund the development 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 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 AKCEA-APO(a)-L_{Rx}; 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, AKCEA-APO(a)-L_{Rx} 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 our partners plan to commercially launch a medicine. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. 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, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx}, the price of our securities could decrease.

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 United States 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.

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, 2019, we had cash, cash equivalents and short-term investments equal to $2.5 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;
- 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.

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

In January 2020, Dr. Crooke, our founder and Chief Executive Officer, transitioned from Chief Executive Officer to Executive Chairman of our Board of Directors. As Executive Chairman, Dr. Crooke will continue to be responsible for the activities of the board and will remain 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 for the last year and has been a member of our team since our founding over 30 years ago, serves as our Chief Executive Officer. 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, Akcea is dependent on the principal members of its staff responsible for marketing, sales and distribution activities. If Akcea is not able to recruit and retain qualified marketing and sales personnel, the sales of TEGSEDI and WAYLIVRA may be adversely affected.

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, 2019, the market price of our common stock ranged from $86.58 to $52.45 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 payors' reimbursement policies, developments in patent or other proprietary rights and public concern regarding the safety of our medicines.

Additionally, broad market and industry factors may 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.

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. 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.

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 percent convertible senior 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.

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.

Changes in tax laws, regulations and treaties could affect our future taxable income.

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.

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 have in the past experienced periods of substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government and the failure, bankruptcy, or sale of various financial and other institutions. 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.

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

On June 23, 2016, the United Kingdom, or the U.K., voted to leave the EU in an advisory referendum, which is generally referred to as Brexit. In January 2020, the U.K. and the EU entered into a withdrawal agreement pursuant to which the U.K. formally withdrew from the EU on January 31, 2020. Following such withdrawal, the U.K. entered into a transition period scheduled to end on December 31, 2020, or the Transition Period. During the Transition Period, the U.K. will remain subject to EU law and maintain access to the EU single market and to the global trade deals negotiated by the EU on behalf of its members. Negotiations are expected to continue in relation to the customs and trading relationship between the U.K. and the EU following the expiry of the Transition Period.

In addition, as a result of Brexit, the EMA, formerly situated in London, relocated to Amsterdam. Following the Transition Period, there is a risk that the relocation will interrupt current administrative routines and occupy resources, which may generally adversely affect our dealings with the EMA. Further, there is considerable uncertainty resulting from a lack of precedent and the complexity of the U.K. and EU's intertwined legal regimes as to how Brexit (following the Transition Period) will impact the life sciences industry in Europe, including our company, including with respect to ongoing or future clinical trials. The impact will largely depend on the model and means by which the U.K.'s relationship with the EU is governed post-Brexit. For example, following the Transition Period, the U.K. will no longer be covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA and, unless a specific agreement is entered into, a separate process for authorization of drug products, including our product candidates, will be required in the UK, the potential process for which is currently unclear. Brexit may adversely affect and delay our ability to commercialize, market and sell our product candidates in the U.K.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 20, 2020, the following are the primary facilities in which we operate:

Property Description	Location	Square Footage	Owned or Leased	Initial Lease Term End Date	Lease Extension Options
Ionis laboratory and office space facility	Carlsbad, CA	176,000	Owned		
Ionis manufacturing facility	Carlsbad, CA	28,700	Owned		
Ionis manufacturing support facility	Carlsbad, CA	25,800	Leased	2021	Two, five-year options to extend
Ionis office space facility	Carlsbad, CA	5,800	Leased	2023	One, five-year option to extend
Akcea office space facility	Boston, MA	30,175	Leased	2028	One, five-year option to extend
Akcea office and Ionis storage space facility	Carlsbad, CA	18,700	Leased	2023	One, five-year option to extend
		285,175			

Item 3. Legal Proceedings

In November 2019, a purported stockholder of Akcea filed an action in the Delaware Court of Chancery, captioned *City of Cambridge Retirement System v. Crooke, et al.*, C.A. No. 2019-0905, 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 stockholders. The plaintiff in the Delaware Action asserts that the Defendants breached their fiduciary duties in connection with the licensing transaction that Akcea and Ionis entered into regarding TEGSEDI and AKCEA-TTR-L_{Rx}. The plaintiff also asserts an unjust enrichment claim against Ionis. We and Akcea have moved to dismiss the plaintiff's complaint. We believe that the claims asserted in the Delaware Action are without merit. The results of litigation are uncertain and entail risk of adverse outcomes, and litigation is usually expensive and can be distracting to management.

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 20, 2020, there were approximately 516 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.

Purchases of Equity Securities

In September 2019, our board of directors approved an initial share repurchase program of up to $125 million of our common stock. Our stock repurchase program has no expiration date. We repurchased the following amounts of our common stock during the fourth quarter of 2019 (in thousands, except per share amounts). All of our repurchases were made under a 10b5-1 plan:

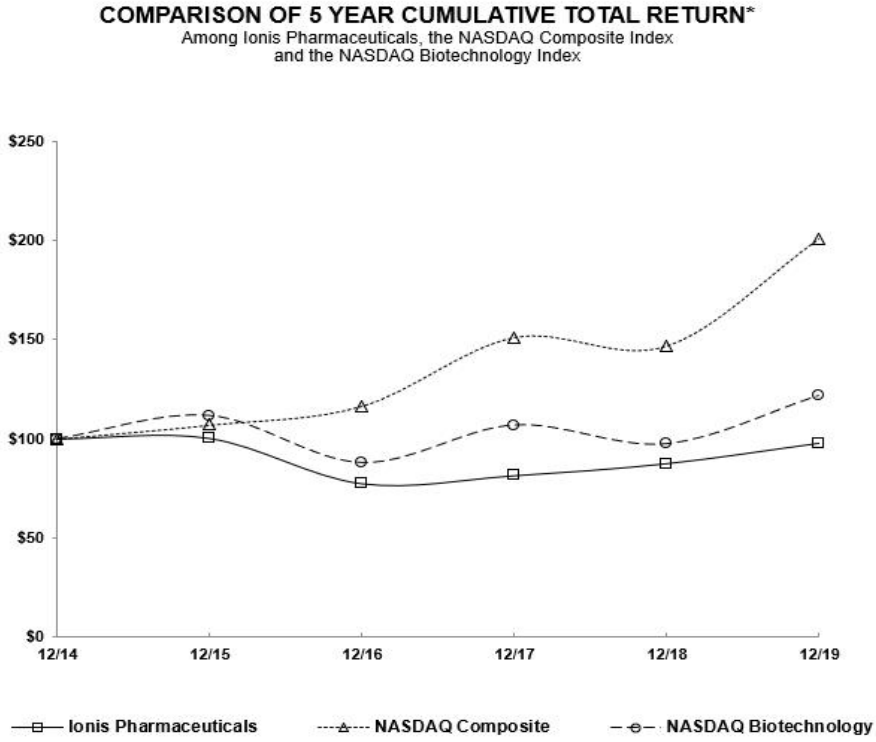
	Total Number of Shares Purchased	Average Price Paid Per Share (1)	Approximate Dollar Value of Shares that May Yet Be Purchased under our Stock Repurchase Program
October 2019	-	$ -	$ 125,000
November 2019	75	63.57	120,230
December 2019	460	64.40	90,593
Total	535		

(1) Average Price Paid Per Share excludes cash paid for commissions.

In the first quarter of 2020, we used the remaining $90.6 million approved under the plan to repurchase additional shares.

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, 2014 in our common stock, the Nasdaq Composite Index (total return) and the Nasdaq Biotechnology Index. The total return assumes reinvestment of dividends.



* $100 invested on December 31, 2014 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

	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18	Dec-19
Ionis Pharmaceuticals, Inc.	$ 100.00	$ 100.31	$ 77.47	$ 81.47	$ 87.56	$ 97.85
Nasdaq Composite Index	$ 100.00	$ 106.96	$ 116.45	$ 150.96	$ 146.67	$ 200.49
Nasdaq Biotechnology Index	$ 100.00	$ 111.77	$ 87.91	$ 106.92	$ 97.45	$ 121.92

(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

This selected financial data should be read in conjunction with our audited consolidated financial statements and accompanying notes and Management's Discussion and Analysis of Financial Condition and Results of Operations included elsewhere in this Annual Report on Form 10-K. Our historical consolidated financial information may not be indicative of our future performance. Set forth below are our selected consolidated financial data (in millions, except per share amounts):

	Years Ended December 31,				
	2019	2018	2017	2016	2015 (1)
Consolidated Statement of Operations Data:					
Revenue	$ 1,122.6	$ 599.7	$ 514.2	$ 372.8	$ 283.7
Research, development and patent expenses	$ 465.7	$ 414.6	$ 374.6	$ 344.3	$ 322.3
Selling, general and administrative expenses	$ 286.6	$ 244.6	$ 108.5	$ 48.6	$ 37.2
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 294.1	$ 273.7	$ 0.3	$ (60.4)	$ (88.3)
Basic net income (loss) per share attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 2.12	$ 2.09	$ 0.15	$ (0.50)	$ (0.74)
Diluted net income (loss) per share attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 2.08	$ 2.07	$ 0.15	$ (0.50)	$ (0.74)
Shares used in computing basic net income (loss) per share	140.0	132.3	124.0	120.9	119.7
Shares used in computing diluted net income (loss) per share	142.9	134.1	126.1	120.9	119.7

	As of December 31,				
	2019	2018	2017	2016 (1)	2015 (1)
Consolidated Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 2,499.5	$ 2,084.1	$ 1,022.7	$ 665.2	$ 779.2
Working capital	$ 2,447.6	$ 1,927.6	$ 925.1	$ 664.1	$ 688.1
Total assets	$ 3,233.1	$ 2,667.8	$ 1,322.8	$ 912.5	$ 947.9
Long-term debt and other obligations, less current portion	$ 1,275.6	$ 1,200.3	$ 713.9	$ 679.1	$ 598.2
Accumulated deficit	$ (707.5)	$ (967.3)	$ (1,241.0)	$ (1,181.4)	$ (1,094.9)
Stockholders' equity	$ 1,684.5	$ 1,187.2	$ 365.3	$ 99.6	$ 200.8

(1) We adopted the new revenue recognition accounting standard in 2018 (Topic 606) and adjusted our 2017 results for the adoption. This change is not reflected in our consolidated statement of operations data for 2015 or in our consolidated balance sheet data for 2016 and 2015.

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 three years in the period ended December 31, 2019, and our financial condition at December 31, 2019. 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

We are a leader in discovering and developing RNA-targeted therapeutics. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics that we believe has fundamentally changed medicine and transformed the lives of people with devastating diseases. Our large, diverse and advancing pipeline has over 40 potential first-in-class and/or best-in-class medicines designed to address a broad spectrum of therapeutic areas, such as neurodegenerative diseases, cardiometabolic diseases, cancer and others. The medicines in our pipeline address patients with diseases ranging from rare to common.

In 2019, we achieved important goals across our business, including advancing four new medicines into pivotal studies. We also reported positive clinical proof-of-concept results from five medicines, four of which were LICA medicines. We advanced and grew our pipeline of unpartnered medicines, which we call our Ionis-owned pipeline. In addition, we made significant progress across the rest of our pipeline by advancing numerous medicines into earlier stages of development, six of which were Ionis-owned medicines. In 2019, we also broadened the scope of our antisense technology by investing in complementary technologies such as new LICA strategies to address more organ systems and cell types and technologies to potentially identify novel targets to ensure continued pipeline growth. These accomplishments enabled us to achieve revenues in excess of $1.1 billion, net income of nearly $300 million and a year-end cash balance of $2.5 billion.

This year we plan to use our financial strength to invest fully in those areas of the business that we believe have the greatest potential to create value for patients and shareholders. By the end of this year, we plan to have six pivotal studies underway and report clinical proof-of-concept data for six or more medicines. We also plan to expand the reach of our antisense technology by optimizing additional routes of administration, such as oral and pulmonary for which we expect clinical data this year. Additionally, this year, we are continuing to prioritize the growth and advancement of our Ionis-owned pipeline. Building on our achievements in 2019, we believe that continued advances in our pipeline and technology will enable us to achieve our goal of 10 or more new drug applications through the end of 2025.

Our goal is to determine the optimal development and commercialization strategy for each medicine in our pipeline, while ensuring we remain focused on innovation and delivering substantial value for patients in need and shareholders. With this goal firmly in mind, this year we plan to further develop our commercial strategy and capabilities to ensure we maximize the value of each of our medicines.

By building on our strong foundation and continuing to focus on our strategic priorities, we believe we are achieving our vision of becoming one of the most successful and innovative companies in the healthcare industry. We intend to continue to pursue our vision by executing on our strategic priorities: advancing our Ionis-owned pipeline, further developing our commercial strategies and capabilities, and expanding the reach of our antisense technology.

We have three commercial medicines approved in major markets around the world, SPINRAZA, TEGSEDI and WAYLIVRA. We have four drugs in pivotal studies, tominersen (formerly IONIS-HTT_{Rx}) for Huntington's disease, tofersen for SOD1-ALS, AKCEA-APO(a)-L_{Rx} for cardiovascular disease, or CVD, and AKCEA-TTR-L_{Rx} for all forms of TTR amyloidosis, or ATTR. Our goal is to start up to five additional pivotal studies before the end of 2021.

SPINRAZA is a 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, 2019, more than 10,000 patients were on SPINRAZA therapy in markets around the world. Additionally, as of December 31, 2019, SPINRAZA is approved in over 50 countries with formal reimbursement in 40 countries. Through December 31, 2019, we have earned more than $1 billion in revenues from our SPINRAZA collaboration, including more than $640 million in royalties on sales of SPINRAZA.

TEGSEDI, a once weekly, self-administered subcutaneous medicine, was approved in 2018 in the U.S., EU and Canada for the treatment of patients with polyneuropathy caused by hereditary TTR amyloidosis, or hATTR, a debilitating, progressive, and fatal disease. Akcea, our majority-owned affiliate focused on developing and commercializing medicines to treat patients with serious and rare diseases, launched TEGSEDI in the U.S. and EU in late 2018. TEGSEDI is commercially available in more than 10 countries. Akcea plans to expand the global launch of TEGSEDI by launching in additional countries. In Latin America, PTC Therapeutics, or PTC, through its exclusive license from Akcea, is launching TEGSEDI in Brazil and is working towards access in additional Latin American countries.

WAYLIVRA, a once weekly, self-administered, subcutaneous medicine, received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. Akcea launched WAYLIVRA in the EU in the third quarter of 2019 and is leveraging its existing commercial infrastructure in Europe to market WAYLIVRA. PTC through its exclusive license agreement with Akcea is working to expand access to WAYLIVRA across Latin America, beginning in Brazil with potential approval in 2020.

Financial Highlights

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

	Year Ended December 31,		
	2019	**2018**	**2017**
Total revenue	$ 1,122.6	$ 599.7	$ 514.2
Total operating expenses	$ 756.7	$ 661.0	$ 483.1
Income (loss) from operations	$ 365.9	$ (61.4)	$ 31.0
Net income (loss)	$ 303.3	$ 215.0	$ (10.8)
Net income attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 294.1	$ 273.7	$ 0.3
Cash, cash equivalents and short-term investments	$ 2,499.5	$ 2,084.1	$ 1,022.7

Our revenue in 2019 nearly doubled, compared to 2018, primarily due to more than doubling our R&D revenues including nearly $490 million in license fees we earned during 2019. Additionally, commercial revenue increased more than 35 percent compared to 2018 primarily from increases in SPINRAZA royalties and TEGSEDI product sales, along with the addition of WAYLIVRA product sales in 2019.

Our operating expenses for 2019 increased compared to 2018, principally due to our investments in the global launches of TEGSEDI and WAYLIVRA and advancing and expanding our pipeline.

We believe we have the financial resources to execute on our strategic priorities for 2020 and beyond. During 2019 we received more than $900 million in payments from our partners.

Business Segments

We have two operating segments, our Ionis Core segment and Akcea Therapeutics, our majority-owned affiliate. Akcea is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with serious and rare diseases. We provide 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 reviews to assess operating performance and to make operating decisions. We allocate a portion of Ionis' development, R&D support and general and administrative expenses to Akcea for work Ionis performs on behalf of Akcea and we bill Akcea for these expenses.

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;
- Income taxes; and
- Estimating the fair value of convertible debt without the conversion feature.

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.

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 2018 and 2019 are 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 2019, we achieved two milestone payments for $7.5 million each under our 2018 strategic neurology collaboration with Biogen. Prior to achieving these milestone payments, we did not consider the payments probable. Upon achieving these milestone payments, we reassessed the total transaction price of our 2018 strategic neurology collaboration. We added these two milestone payments 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 API 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. For example, in the fourth quarter of 2019, we completed our R&D services performance obligation under our collaboration with Biogen for new antisense medicines for the treatment of SMA sooner than we anticipated. 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. As a result of completing our performance obligation earlier than our previous estimate, we recognized $8.3 million of additional revenue in the fourth quarter of 2019.

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

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. 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

For U.S. federal income tax purposes, we are required to file separate U.S. federal income tax returns for Ionis and Akcea. We began deconsolidating Akcea for U.S. federal income tax purposes upon Akcea's IPO. As a result, we are 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. We continue to file combined state tax returns in most jurisdictions. As a result, we continue to assess the state portion of our valuation allowance for those jurisdictions on a consolidated basis.

We have historically recorded a valuation allowance against all our net deferred tax assets due to cumulative financial statement losses. However, in the fourth quarter of 2018, we reversed the valuation allowance previously recorded against our Ionis stand-alone U.S. federal net deferred tax assets, resulting in a one-time non-cash tax benefit of $332.1 million. We reversed this valuation allowance in 2018 based on Ionis' stand-alone pre-tax income in that period and our expectation to generate sufficient stand-alone pre-tax income in future years to fully utilize our U.S. federal net operating loss carryforwards and our R& D and Orphan Drug tax credit carryforwards over the next three years. We utilized a significant portion of these carryforwards in 2019 to reduce our estimated federal tax liability for the year.

We continue to maintain a full valuation allowance of $197.0 million against all of Akcea's net deferred tax assets and the net state deferred tax assets of Ionis at December 31, 2019 due to uncertainties related to our ability to realize the tax benefits associated with these assets. We maintain a full valuation allowance against Akcea's stand-alone net deferred tax assets primarily due to Akcea's history of financial statement losses and the uncertainty of generating sufficient pre-tax income in future periods to realize the deferred tax benefits. We maintain a full valuation allowance against the net state deferred tax assets of Ionis as we file combined state tax returns with Akcea in most jurisdictions, which includes the impact of Akcea's historical losses.

We generated combined state taxable income and recognized a combined state tax liability in 2019. We utilized Ionis' state deferred tax assets, primarily California net operating loss carry forwards, to reduce our combined state tax liability by $59.1 million, which resulted in a corresponding reduction to our combined state valuation allowance. We have historically generated combined state net operating losses due primarily to Akcea's net operating losses. However, Akcea generated net income in 2019. This was due to an increase in their research and development and license revenue, primarily related to non-recurring transactions in the first and fourth quarter from Novartis' exercise of its option to license AKCEA-APO(a)-L_{Rx} and Pfizer's license of AKCEA-ANGPTL3-L_{Rx}, respectively. Although Akcea generated net income in 2019, given their history of losses, there can be no assurance that they will achieve profitability in future periods. We expect Akcea to incur additional operating losses for the foreseeable future and therefore we continue to maintain a full valuation allowance against our remaining net deferred state 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.

Estimating the Fair Value of Convertible Debt Without the Conversion Feature

In December 2019, we issued new convertible senior notes, which we refer to as our 0.125% Notes. To account for the issuance of the 0.125% Notes, which may be settled in cash upon conversion (including partial cash settlement), we are required to separate the liability and equity components of the 0.125% Notes in a manner that reflects our nonconvertible debt borrowing rate at issuance. In reviewing recent debt issuances, we were not able to identify any comparable companies that recently issued non-convertible debt instruments. Therefore, we estimated the fair value of the liability component of our 0.125% 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 used the average of our estimated underlying credit rate and observable credit spreads for comparable companies with similar debt outstanding plus the London Inter-Bank Offered Rate, or LIBOR, swap rate for the same maturity time period as our 0.125% Notes (five years). These estimates and assumptions were judgmental in nature and had a significant impact on the determination of the liability component and the associated non-cash interest expense. For additional information, see Note 3, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements.

Results of Operations

Below we have included our results of operations for 2019 compared to 2018. Refer to our 2018 Form 10-K for our results of operations for 2018 compared to 2017.

Years Ended December 31, 2019 and December 31, 2018

Revenue

Total revenue for 2019 was $1.1 billion, compared to $599.7 million in 2018 and was comprised of the following (amounts in thousands):

	Year Ended December 31,	
	2019	**2018**
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 292,992	$ 237,930
Product sales, net	42,253	2,237
Licensing and other royalty revenue	17,205	14,755
Total commercial revenue	352,450	254,922
R&D revenue:		
Amortization from upfront payments	146,246	124,695
Milestone payments	114,906	82,771
License fees	489,708	102,053
Other services	19,289	35,233
Total R&D revenue	770,149	344,752
Total revenue	$ 1,122,599	$ 599,674

We significantly increased both commercial and R&D revenue in 2019, compared to 2018. Commercial revenue increased over 35 percent primarily due to increased SPINRAZA royalties and TEGSEDI product sales. We launched WAYLIVRA in the third quarter of 2019.

Our R&D revenue more than doubled in 2019 compared to 2018. The most significant components were:

- $246 million we earned from Pfizer when Pfizer licensed AKCEA-ANGPTL3-L_{Rx};
- $150 million we earned from Novartis when Novartis licensed AKCEA-APO(a)-L_{Rx};
- $136 million we earned from Biogen for advancing several programs under our collaborations, including adding four targets under our 2018 strategic neurology collaboration;
- $45 million we earned from Biogen when Biogen licensed IONIS-$MAPT_{Rx}$;
- $35 million we earned from Roche when Roche enrolled the first patient in the Phase 3 study of tominersen in patients with Huntington's disease;
- $25 million we earned from GSK when GSK licensed our HBV program; and
- $20 million we earned from Alnylam when Alnylam licensed our technology to Regeneron.

Operating Expenses

Operating expenses for 2019 were $756.7 million, and increased compared to $661.0 million for 2018. R&D expenses for 2019 increased compared to 2018 primarily from investments we made in our technology and advancing and expanding our pipeline. Additionally, our SG&A expenses increased in 2019 compared to 2018 principally due to our investment in the global launches of TEGSEDI and WAYLIVRA and various SG&A expenses we incurred related to the growth in our business.

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

	Year Ended December 31,	
	2019	2018
Ionis Core	$ 374,014	$ 293,175
Akcea Therapeutics	450,688	251,408
Elimination of intercompany activity	(214,560)	(14,849)
Subtotal	610,142	529,734
Non-cash compensation expense related to equity awards	146,574	131,312
Total operating expenses	$ 756,716	$ 661,046

Akcea's operating expenses included $200 million of intercompany drug development expenses consisting of the $75 million sublicense fee for Novartis' license of AKCEA-APO(a)-L_{Rx} and the $125 million sublicense fee for Pfizer's license of AKCEA-ANGPTL3-L_{Rx}. We eliminated these expenses in our consolidated results.

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 (beginning in the third quarter of 2019) and certain associated period costs. We do not expect our fixed costs will increase in direct correlation to TEGSEDI and WAYLIVRA product sales. 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 Akcea is 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 thousands):

	Year Ended December 31,	
	2019	2018
Ionis Core	$ —	$ —
Akcea Therapeutics	12,820	11,573
Elimination of intercompany activity	(8,873)	(9,913)
Subtotal	3,947	1,660
Non-cash compensation expense related to equity awards	437	160
Total cost of products sold	$ 4,384	$ 1,820

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 2019 compared to 2018 primarily due to the increase in commercial product sales. We previously expensed $0.7 million and $0.1 million of costs to produce the TEGSEDI and WAYLIVRA we sold in 2019 and 2018, respectively. We recognized these costs in prior periods because we incurred these costs before we obtained regulatory approval. 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. Akcea is recognizing this amortization over TEGSEDI's remaining estimated patent life. We eliminate this amortization in our consolidated results. 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 developmental chemistry and R&D support expenses.

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

	Year Ended December 31,	
	2019	2018
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 370,340	$ 338,047
Non-cash compensation expense related to equity awards	95,348	76,557
Total research, development and patent expenses	$ 465,688	$ 414,604

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

	Year Ended December 31,	
	2019	2018
Ionis Core	$ 295,071	$ 222,528
Akcea Therapeutics	280,956	120,905
Elimination of intercompany activity	(205,687)	(5,386)
Subtotal	370,340	338,047
Non-cash compensation expense related to equity awards	95,348	76,557
Total research, development and patent expenses	$ 465,688	$ 414,604

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 and our partners' drug pipelines.

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

	Year Ended December 31,	
	2019	2018
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 83,506	$ 61,387
Non-cash compensation expense related to equity awards	20,913	17,530
Total antisense drug discovery expenses	$ 104,419	$ 78,917

Antisense drug discovery expenses were higher in 2019, compared to 2018, due to expenses we incurred related to advancing our research programs and investments we made in complementary technologies to expand the reach of 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 medicines in Phase 3 development and/or commercialization for which we have incurred significant costs (in thousands):

	Year Ended December 31,	
	2019	2018
AKCEA-TTR-L_{Rx}	$ 14,061	$ 3,204
WAYLIVRA	7,435	19,397
TEGSEDI	16,830	19,204
Other antisense development projects	94,188	98,546
Development overhead expenses	74,006	63,940
Total antisense drug development, excluding non-cash compensation expense related to equity awards	206,520	204,291
Non-cash compensation expense related to equity awards	45,898	34,845
Total antisense drug development expenses	$ 252,418	$ 239,136

Our development expenses were essentially flat in 2019 compared to 2018. In 2019, we had increased expenses related to AKCEA-TTR-L_{Rx} and overhead expenses to support the investments we are making in advancing our pipeline, including our Ionis-owned pipeline. These increases were mostly offset by decreases in expenses from WAYLIVRA, TEGSEDI and AKCEA-APO(a)-L_{Rx}. Expenses related to AKCEA-APO(a)-L_{Rx} decreased because we completed our Phase 2 study and Novartis is responsible for all further development activities. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2019	2018
Ionis Core	$ 145,062	$ 100,090
Akcea Therapeutics	261,458	104,201
Elimination of intercompany activity	(200,000)	—
Subtotal	206,520	204,291
Non-cash compensation expense related to equity awards	45,898	34,845
Total antisense drug development expenses	$ 252,418	$ 239,136

Akcea's development expenses included $200 million of intercompany drug development expenses consisting of the $75 million sublicense fee for Novartis' license of AKCEA-APO(a)-L_{Rx} and the $125 million sublicense fee for Pfizer's license of AKCEA-ANGPTL3-L_{Rx}. We eliminated these expenses in our consolidated results. Excluding these fees, Akcea's development expenses decreased primarily because Akcea transitioned all further development of AKCEA-APO(a)-L_{Rx} to Novartis.

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 Developmental Chemistry

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

Our manufacturing and developmental chemistry expenses were as follows (in thousands):

	Year Ended December 31,	
	2019	2018
Manufacturing and developmental chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 42,507	$ 39,806
Non-cash compensation expense related to equity awards	9,569	9,036
Total manufacturing and developmental chemistry expenses	$ 52,076	$ 48,842

Our manufacturing and developmental chemistry expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2019	2018
Ionis Core	$ 36,847	$ 32,277
Akcea Therapeutics	11,174	12,758
Elimination of intercompany activity	(5,515)	(5,229)
Subtotal	42,507	39,806
Non-cash compensation expense related to equity awards	9,569	9,036
Total manufacturing and developmental chemistry expenses	$ 52,076	$ 48,842

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 thousands):

	Year Ended December 31,	
	2019	2018
Personnel costs	$ 15,165	$ 12,968
Occupancy	9,351	8,567
Patent expenses	4,209	2,744
Depreciation and amortization	519	439
Insurance	1,861	1,622
Other	6,703	6,223
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	37,808	32,563
Non-cash compensation expense related to equity awards	18,968	15,146
Total R&D support expenses	$ 56,776	$ 47,709

R&D support expenses for 2019 were slightly higher compared to 2018 primarily due to costs from the growth of Akcea's business as they continued to expand. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2019	2018
Ionis Core	$ 29,656	$ 28,774
Akcea Therapeutics	8,324	3,946
Elimination of intercompany activity	(172)	(157)
Subtotal	37,808	32,563
Non-cash compensation expense related to equity awards	18,968	15,146
Total R&D support expenses	$ 56,776	$ 47,709

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 thousands):

	Year Ended December 31,	
	2019	2018
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 235,856	$ 190,027
Non-cash compensation expense related to equity awards	50,788	54,595
Total selling, general and administrative expenses	$ 286,644	$ 244,622

SG&A expenses were higher for 2019 compared to 2018 principally due to the cost of commercializing TEGSEDI and WAYLIVRA and various other expenses related to the growth in our business. All amounts exclude non-cash compensation expense related to equity awards.

Our selling, general and administrative expenses by segment were as follows (in thousands):

	Year Ended December 31,	
	2019	2018
Ionis Core	$ 78,943	$ 70,647
Akcea Therapeutics	156,912	118,930
Elimination of intercompany activity	—	450
Subtotal	235,855	190,027
Non-cash compensation expense related to equity awards	50,789	54,595
Total selling general and administrative expenses	$ 286,644	$ 244,622

Akcea Therapeutics, Inc.

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

	Year Ended December 31,	
	2019	2018
Cost of products sold	$ 12,819	$ 11,573
Development and patent expenses	80,956	120,905
Sublicense fees to Ionis	200,000	—
Selling, general and administrative expenses	156,912	118,930
Profit (loss) share for TEGSEDI commercialization activities	(37,332)	—
Total operating expenses, excluding non-cash compensation expense related to equity awards	413,355	251,408
Non-cash compensation expense related to equity awards	37,111	44,275
Total Akcea Therapeutics operating expenses	$ 450,466	$ 295,683

Akcea's development and patent expenses increased in 2019 compared to 2018 as a result of sublicense fees totaling $200 million Akcea paid to Ionis in Akcea common stock for Ionis' portion of the license fee Akcea received from Novartis in the first quarter of 2019 and from Pfizer in the fourth quarter of 2019. We eliminated the sublicense fees Akcea paid Ionis in our consolidated results. Excluding these fees, Akcea's development expenses decreased primarily because Akcea transitioned all further development of AKCEA-APO(a)-L_{Rx} to Novartis.

Akcea's SG&A expenses increased in 2019, compared to 2018, primarily due to Akcea's commercialization of TEGSEDI and WAYLIVRA. For each period presented, we allocated a portion of Ionis' SG&A expenses to Akcea for work we performed on Akcea's behalf and we bill Akcea for these expenses. We included these allocated expenses in Akcea's SG&A expenses in the table above. All amounts exclude non-cash compensation expense related to equity awards.

In the first quarter of 2019, we began sharing profits and losses for TEGSEDI with Akcea under our TTR licensing agreement. As Akcea is the principal for all commercial activities related to the TTR License Agreement, Akcea records all activities related to TEGSEDI on a gross basis in its statement of operations based on the nature of the activity, including revenues, cost of products sold and sales and marketing expenses. Ionis' share of the net profit/loss from commercializing TEGSEDI is separately presented on Akcea's statement of operations on the line titled "Profit (loss) share for TEGSEDI commercialization activities". Since TEGSEDI is currently generating a loss, this represents the amount Ionis owes Akcea under the licensing agreement for Ionis' share of the net loss of TEGSEDI commercialization activities during the period. In 2019, Ionis' share of losses for TEGSEDI commercialization activities was $37 million. With the launch of WAYLIVRA in the third quarter of 2019, Akcea began paying Ionis royalties on WAYLIVRA product sales. We eliminate these amounts in our consolidated results.

All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for 2019 was $52.2 million compared to $30.2 million for 2018. Investment income increased primarily due to a significantly higher average cash balance and higher average returns.

Interest Expense

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

	Year Ended December 31,	
	2019	2018
Convertible senior notes:		
Non-cash amortization of the debt discounts and debt issuance costs	$ 39,280	$ 35,173
Interest expense payable in cash	6,727	6,855
Interest on mortgage for primary R&D and manufacturing facilities	2,397	2,409
Other	364	352
Total interest expense	$ 48,768	$ 44,789

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 $43.5 million for 2019, compared to an income tax benefit of $291.1 million for 2018**.** Our income tax expense in 2019 relates primarily to our estimated U.S. federal and state tax liabilities for the year. We recognized a significant tax benefit in 2018 due largely to a one-time, non-cash tax benefit from the reversal of the valuation allowance previously recorded against Ionis' stand-alone U.S. federal net deferred tax assets of $332.1 million. We reversed the valuation allowance in 2018 as we determined it was more likely than not that we would utilize our deferred federal income tax assets, primarily net operating loss carryforwards and research and development and orphan drug credit carryforwards, in future years. We utilized a significant portion of these carryforwards in 2019 to reduce our estimated federal tax liability for the year. We continue to maintain a full valuation allowance against all of Akcea's net deferred tax assets and the net state deferred tax assets of Ionis at December 31, 2019 due to uncertainties related to our ability to realize the tax benefits associated with these assets. See discussion of our valuation allowance under the section titled, *Income Taxes*, above in our discussion of our critical accounting estimates.

Net Income

We had net income of $303.3 million for 2019, compared to $215.0 million for 2018. The increase in our net income in 2019, compared to 2018 was primarily due to our increasing revenues. Somewhat offsetting this increase was income tax expense we recognized in 2019 compared to a one-time non-cash tax benefit recognized in 2018 related to our deferred income taxes.

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

At December 31, 2019, we owned approximately 76 percent of Akcea. The shares of Akcea third parties own represent an interest in Akcea's equity that we do not control. However, because we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our consolidated financial statements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line called "Net income attributable to noncontrolling interest in Akcea" on our statement of operations. Our noncontrolling interest in Akcea on our statement of operations for 2019 was net income of $9.1 million, compared to a net loss of $58.8 million for 2018. Akcea generated net income in 2019 primarily because it earned significant license fee revenue from Novartis and Pfizer.

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

We had net income attributable to our common stockholders of $294.1 million for 2019, compared $273.7 million in 2018. Basic and diluted net income per share for 2019 was $2.12 and $2.08, respectively compared to $2.09 and $2.07 for 2018. The increase in our net income attributable to our common stockholders in 2019, compared to 2018, was primarily due to our increasing revenues. Somewhat offsetting this increase was income tax expense we recognized in 2019 compared to a one-time non-cash tax benefit recognized in 2018 related to our deferred income taxes.

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, 2019, we had earned approximately $4.3 billion in revenue. We 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, 2019, we had raised net proceeds of approximately $1.8 billion from the sale of our equity securities, not including the $182.4 million Akcea received in net proceeds from its IPO in July 2017. Additionally, we borrowed approximately $1.5 billion under long-term debt arrangements to finance a portion of our operations over the same time period.

At December 31, 2019, we had cash, cash equivalents and short-term investments of $2.5 billion and stockholders' equity of $1.7 billion. In comparison, we had cash, cash equivalents and short-term investments of $2.1 billion and stockholders' equity of $1.2 billion at December 31, 2018. Our cash, cash equivalents and short-term investments increased in 2019 primarily from payments we received from Biogen, Pfizer, Novartis and Roche. Our stockholders' equity increased in 2019 primarily from our net income and our stock-based compensation expense.

In September 2019, our board of directors approved an initial share repurchase program of up to $125 million of our common stock. Our stock repurchase program has no expiration date. Through December 31, 2019, we had repurchased 535,000 shares for $34.4 million in open market transactions. See *Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities* for details of the purchases we made in 2019. During the first quarter of 2020, we repurchased the remaining amount authorized under our stock repurchase program. We may consider additional share repurchases in the future as part of our overall capital allocation strategy.

At December 31, 2019, we had consolidated working capital of $2.4 billion compared to $1.9 billion at December 31, 2018. As of December 31, 2019, our debt and other obligations totaled $936.2 million compared to $764.0 million at December 31, 2018. In December 2019, we exchanged $375.6 million of our 1% notes for $439.3 million of new 0.125% notes and issued an additional $109.5 million of new 0.125% notes. Additionally, during 2019 our debt and other obligations increased from the operating lease liability we added to our balance sheet when we adopted the new accounting guidance for leases on January 1, 2019.

The following table summarizes our contractual obligations as of December 31, 2019. 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:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
1% Notes (principal and interest payable)	$ 316.1	$ 3.1	$ 313.0	$ —	$ —
0.125% Notes (principal and interest payable)	$ 552.3	$ 0.7	$ 1.4	$ 550.2	$ —
Building mortgage payments	$ 78.2	$ 2.4	$ 5.1	$ 6.9	$ 63.8
Other obligations (principal and interest payable)	$ 1.0	$ 0.1	$ 0.1	$ 0.1	$ 0.7
Operating leases	$ 23.5	$ 3.3	$ 5.8	$ 4.9	$ 9.5
Total	$ 971.1	$ 9.6	$ 325.4	$ 562.1	$ 74.0

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 flows 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.

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% 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.

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 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, 2019, we had the following 0.125% Notes outstanding (amounts in millions except price per share data):

	0.125% Notes
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. 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 new 0.125% Notes. As a result, the principal balance of the 1% Notes following the exchange was $309.9 million.

At December 31, 2019, we had the following 1% Notes outstanding (amounts in millions except price per share data):

	1% Notes
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.

Financing 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.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2019 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.

Off-Balance Sheet Arrangements

We have not entered into, nor do we currently have, any off-balance sheet arrangements (as defined under SEC rules).

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, 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, 2019.

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, 2019, 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, 2019.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2019, 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, 2019, 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, 2019, 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, 2019 and 2018, and the related consolidated statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2019, and the related notes and our report dated March 2, 2020 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 US 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
March 2, 2020

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, 2019 (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.

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

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, 2019.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders (a)	11,001,241	$ 51.48	8,335,635(b)
Total	11,001,241	$ 51.48	8,335,635

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

(b) Of these shares, 725,930 remained available for purchase under the ESPP as of December 31, 2019.

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

Exhibit Number	Description of Document
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 August 13, 2012, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 2¾ percent Convertible Senior Note due 2019, filed as an exhibit to the Registrant's Report on Form 8-K filed August 13, 2012 and incorporated herein by reference.
4.4	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.
4.5	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.
4.6	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.
4.7	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.
4.8	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.
4.9	Description of the Registrant's Securities.
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 Form8-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	Collaboration and License Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001, filed as an exhibit to the Registrant's report on Form 10-Q as amended for the quarter ended June 30, 2001 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	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.
10.7	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.
10.8	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.
10.9	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.
10.10	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.
10.11*	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 2014 Annual Meeting of Stockholders, filed with the SEC on April 25, 2014, and incorporated herein by reference.
10.12*	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 Quarterly Report on Form 10-Q for the quarter ended June 30, 2012 and incorporated herein by reference.
10.13	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.
10.14*	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.
10.15*	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.
10.16*	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.
10.17	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.
10.18*	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.
10.19*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2004 and incorporated herein by reference.

10.20	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.
10.21	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.
10.22	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.
10.23	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.
10.24	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.
10.25	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.
10.26	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.
10.27	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.
10.28	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.
10.29	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.
10.30	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.
10.31	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.
10.32	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.

10.33	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.
10.34	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.
10.35	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.
10.36	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.
10.37	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.
10.38	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.
10.39	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.
10.40	Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 22, 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.
10.41	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.
10.42	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.
10.43	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.
10.44	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.

10.45	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.
10.46	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.
10.47	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.
10.48	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.
10.49	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.
10.50	First Amendment to Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 21, 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.
10.51	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.
10.52	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.
10.53	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.
10.54	Environmental Indemnity Agreement among the Registrant, 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.
10.55*	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.
10.56	Second Amended and Restated Strategic Advisory Services Agreement by and between the Registrant and B. Lynne Parshall, dated January 9, 2020, filed as an exhibit to the Registrant's Current Report on Form 8-K filed January 10, 2020 and incorporated herein by reference.
10.57	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.
10.58	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.
10.59	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.

10.60	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.
10.61	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.
10.62	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.
10.63	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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.64	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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.65	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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.66	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.
10.67	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. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.68	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. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.69	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.
10.70	Letter Agreement between the Registrant, Akcea Therapeutics, Inc., and Pfizer Inc., dated October 4, 2019. 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, 2019, 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 133, 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 2nd day of March, 2020.

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.

Signatures	Title	Date
/s/ BRETT P. MONIA Brett P. MONIA, Ph.D.	Director and Chief Executive Officer (Principal executive officer)	March 2, 2020
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	March 2, 2020
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Executive Chairman of the Board	March 2, 2020
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director and Senior Strategic Advisor	March 2, 2020
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	March 2, 2020
/s/ BREAUX CASTLEMAN Breaux Castleman	Director	March 2, 2020
/s/ MICHAEL HAYDEN Michael Hayden, CM OBC MB ChB PhD FRCP(C) FRSC	Director	March 2, 2020
/s/ JOAN E. HERMAN Joan E. Herman	Director	March 2, 2020
/s/ JOSEPH KLEIN Joseph Klein, III	Director	March 2, 2020
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Director	March 2, 2020
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	March 2, 2020
/s/ PETER N. REIKES Peter N. Reikes	Director	March 2, 2020
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	March 2, 2020

IONIS PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

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, 2019 and 2018, 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, 2019 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, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, in conformity with US 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, 2019, 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 March 2, 2020 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 Matters

The critical audit matters communicated below are matters arising from the current period audit of the financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matters below, providing a separate opinion on the critical audit matters or on the accounts or disclosures to which they relate.

	Revenue recognition for collaboration agreements
Description of the Matter	For the year ended December 31, 2019, the Company's reported research and development revenue under collaborative agreements was $770.1 million. As discussed in Note 1 to the consolidated financial statements, the Company enters into collaboration agreements that are often comprised of multiple performance obligations, including technology licenses or options to obtain technology licenses, research and development services, and manufacturing services. Auditing the Company's revenue recognition for collaboration agreements is complex because significant judgment may be required to apply the authoritative accounting guidance at the outset of the arrangement, including the determination of performance obligations and transaction price, as well as the allocation of the transaction price among the performance obligations. For example, the allocation of the transaction price among the performance obligations involves the estimation of the standalone selling price of each performance obligation which is based upon various assumptions, which may include projected income, estimated costs and discount rate.

How We Addressed the Matter in Our Audit

We evaluated and tested the design and operating effectiveness of key controls over the risks of material misstatement relating to the accounting for revenue recognition of collaboration agreements with multiple performance obligations. For example, we tested management's controls over the allocation of the transaction price, particularly the review of the methodology and assumptions used in the valuation of standalone selling price mentioned above.

Our audit procedures included, among others, evaluating the Company's assessment of the authoritative guidance to its contracts, inspecting contracts entered into during the period, and evaluating management's interpretation of certain contract provisions when identifying performance obligations and allocating the transaction price to the performance obligations. We also evaluated the Company's key assumptions and judgments and tested the completeness and accuracy of the underlying data used to determine the standalone selling price of each performance obligation. In addition, we compared the significant assumptions mentioned above to current industry and market trends and performed sensitivity analyses to evaluate the changes to revenue recognized that would result from changes in the assumptions.

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, 2019, the Company had gross deferred tax assets of $514.5 million and a related valuation allowance of $197.0 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.

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 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 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.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 1989

San Diego, California
March 2, 2020

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

	December 31,	
	2019	**2018**
ASSETS		
Current assets:		
Cash and cash equivalents	$ 683,287	$ 278,820
Short-term investments	1,816,257	1,805,252
Contracts receivable	63,034	12,759
Inventories	18,180	8,582
Other current assets	139,839	102,473
Total current assets	2,720,597	2,207,886
Property, plant and equipment, net	153,651	132,160
Patents, net	25,674	24,032
Long-term deferred tax assets	305,557	290,796
Deposits and other assets	27,633	12,910
Total assets	$ 3,233,112	$ 2,667,784
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 16,067	$ 28,660
Accrued compensation	37,357	29,268
Accrued liabilities	66,769	47,503
Income taxes payable	32,514	858
Current portion of long-term obligations	2,026	13,749
Current portion of deferred contract revenue	118,272	160,256
Total current liabilities	273,005	280,294
Long-term deferred contract revenue	490,060	567,359
0.125 percent convertible senior notes	434,711	—
1 percent convertible senior notes	275,333	568,215
Long-term obligations, less current portion	15,543	4,914
Long-term mortgage debt	59,913	59,842
Total liabilities	1,548,565	1,480,624
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 140,339,615 and 137,928,828 shares issued and outstanding at December 31, 2019 and December 31, 2018, respectively	140	138
Additional paid-in capital	2,203,778	2,047,250
Accumulated other comprehensive loss	(25,290)	(32,016)
Accumulated deficit	(707,534)	(967,293)
Total Ionis stockholders' equity	1,471,094	1,048,079
Noncontrolling interest in Akcea Therapeutics, Inc.	213,453	139,081
Total stockholders' equity	1,684,547	1,187,160
Total liabilities and stockholders' equity	$ 3,233,112	$ 2,667,784

See accompanying notes.

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

	Year Ended December 31,		
	2019	**2018**	**2017**
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 292,992	$ 237,930	$ 112,540
Product sales, net	42,253	2,237	—
Licensing and other royalty revenue	17,205	14,755	7,474
Total commercial revenue	352,450	254,922	120,014
Research and development revenue under collaborative agreements	770,149	344,752	394,165
Total revenue	1,122,599	599,674	514,179
Expenses:			
Cost of products sold	4,384	1,820	—
Research, development and patent	465,688	414,604	374,644
Selling, general and administrative	286,644	244,622	108,488
Total operating expenses	756,716	661,046	483,132
Income (loss) from operations	365,883	(61,372)	31,047
Other income (expense):			
Investment income	52,205	30,187	8,179
Interest expense	(48,768)	(44,789)	(44,752)
Loss on extinguishment of financing liability for leased facility	—	—	(7,689)
Loss on early retirement of debt	(21,865)	—	—
Other expenses	(686)	(182)	(3,548)
Income (loss) before income tax benefit (expense)	346,769	(76,156)	(16,763)
Income tax benefit (expense)	(43,507)	291,141	5,980
Net income (loss)	303,262	214,985	(10,783)
Net (income) loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	(9,116)	58,756	11,129
Net income attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 294,146	$ 273,741	$ 346
Basic net income per share	$ 2.12	$ 2.09	$ 0.15
Shares used in computing basic net income per share	139,998	132,320	124,016
Diluted net income per share	$ 2.08	$ 2.07	$ 0.15
Shares used in computing diluted net income per share	142,872	134,056	126,098

See accompanying notes.

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

	Year Ended December 31,		
	2019	**2018**	**2017**
Net income (loss)	$ 303,262	$ 214,985	$ (10,783)
Unrealized gains (losses) on investments, net of tax	6,633	(280)	(960)
Reclassification adjustment for realized gains included in net income (loss)	—	—	(374)
Currency translation adjustment	93	23	(67)
Comprehensive income (loss)	309,988	214,728	(12,184)
Comprehensive income (loss) attributable to noncontrolling interest in Akcea Therapeutics, Inc.	9,118	(58,781)	(11,224)
Comprehensive income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 300,870	$ 273,509	$ (960)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2019, 2018 and 2017
(In thousands)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at December 31, 2016	121,636	$ 122	$ 1,311,229	$ (30,358)	$ (1,241,380)	$ 39,613	$ —	$ 39,613
Net income	—	—	—	—	346	346	—	346
Change in unrealized gains, net of tax	—	—	—	(1,334)	—	(1,334)	—	(1,334)
Foreign currency translation	—	—	—	(67)	—	(67)	—	(67)
Novartis stock purchase	1,631	2	71,737	—	—	71,739	—	71,739
Issuance of common stock in connection with employee stock plans	1,709	1	22,931	—	—	22,932	—	22,932
Stock-based compensation expense	—	—	85,975	—	—	85,975	—	85,975
Issuance of Akcea Therapeutics, Inc. common stock in conjunction with initial public offering	—	—	157,270	—	—	157,270	—	157,270
Noncontrolling interest in Akcea Therapeutics, Inc. in conjunction with initial public offering	—	—	(90,351)	—	—	(90,351)	90,381	30
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(5,110)	—	—	(5,110)	(6,114)	(11,224)
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	137,929	$ 138	$ 2,047,250	$ (32,016)	$ (967,293)	$ 1,048,079	$ 139,081	$ 1,187,160
Net income	—	—	—	—	294,146	294,146	—	294,146
Change in unrealized gains, 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	140,340	$ 140	$ 2,203,778	$ (25,290)	$ (707,534)	$ 1,471,094	$ 213,453	$ 1,684,547

See accompanying notes.

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

	Year Ended December 31,		
	2019	**2018**	**2017**
Operating activities:			
Net income (loss)	$ 303,262	$ 214,985	$ (10,783)
Adjustments to reconcile net income (loss) to net cash provided by operating activities:			
Depreciation	12,540	10,706	6,708
Amortization of right-of-use operating lease assets	1,542	—	—
Amortization of patents	1,912	1,822	1,641
Amortization of premium (discount) on investments, net	(7,485)	(1,013)	6,752
Amortization of debt issuance costs	1,942	1,810	1,616
Amortization of convertible senior notes discount	37,338	33,363	30,920
Amortization of long-term financing liability for leased facility	—	—	3,659
Stock-based compensation expense	146,574	131,312	85,975
Gain on investment in Regulus Therapeutics, Inc.	—	—	(374)
Loss on extinguishment of financing liability for leased facility	—	—	7,689
Loss on early retirement of debt	21,865	—	—
Deferred income taxes (including benefit from valuation allowance release)	(7,096)	(290,516)	—
Non-cash losses related to patents, licensing, property, plant and equipment and investments	2,034	1,012	3,302
Changes in operating assets and liabilities:			
Contracts receivable	(47,674)	47,595	45,088
Inventories	(5,411)	1,400	(2,493)
Other current and long-term assets	(44,659)	(29,348)	(58,367)
Long-term income tax receivable	8,418	(223)	(9,114)
Accounts payable	(16,343)	(655)	1,784
Income taxes	31,656	(710)	435
Accrued compensation	8,089	4,117	965
Accrued liabilities and deferred rent	16,499	(17,023)	28,564
Deferred contract revenue	(119,283)	494,254	30,182
Net cash provided by operating activities	345,720	602,888	174,149
Investing activities:			
Purchases of short-term investments	(1,946,726)	(1,794,735)	(877,810)
Proceeds from the sale of short-term investments	1,951,734	882,824	557,369
Purchases of property, plant and equipment	(30,905)	(13,608)	(34,764)
Acquisition of licenses and other assets, net	(5,377)	(4,044)	(3,093)
Purchase of strategic investments	(10,000)	—	(2,500)
Proceeds from the sale of Regulus Therapeutics, Inc.	—	—	2,507
Net cash (used in) provided by investing activities	(41,274)	(929,563)	(358,291)
Financing activities:			
Proceeds from equity, net	119,657	27,900	22,931
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(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	(34,392)	—	—
Principal payments on debt and capital lease obligations	(12,500)	—	(3,599)
Proceeds from issuance of common stock in Akcea Therapeutics, Inc. from its initial public offering, net of underwriters' discount	—	—	110,438
Proceeds from building mortgage debt, net of issuance costs	—	—	59,750
Proceeds from the issuance of common stock to Biogen	—	447,965	—
Proceeds from the issuance of common stock to Novartis	—	—	71,737
Proceeds from the sale of Akcea Therapeutics, Inc. common stock to Novartis in a private placement	—	—	50,000
Offering costs paid	—	—	(2,037)
Payment to settle financing liability for leased facility	—	—	(80,133)
Net cash provided by financing activities	100,021	475,865	229,087
Net increase in cash and cash equivalents	404,467	149,190	44,945
Cash and cash equivalents at beginning of year	278,820	129,630	84,685
Cash and cash equivalents at end of year	$ 683,287	$ 278,820	$ 129,630

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

	Year Ended December 31,		
	2019	**2018**	**2017**
Supplemental disclosures of cash flow information:			
Interest paid	$ 9,870	$ 9,592	$ 8,035
Income taxes paid	$ 9,041	$ —	$ —
Supplemental disclosures of non-cash investing and financing activities:			
Right-of-use assets obtained in exchange for lease liabilities	$ 14,178	$ —	$ —
Amounts accrued for capital and patent expenditures	$ 3,126	$ 4,428	$ 1,983
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.

1. Organization and Significant Accounting Policies

Basis of Presentation

In our consolidated financial statements we included the accounts of Ionis Pharmaceuticals, Inc. ("we", "us" or "our") and the consolidated results of our majority-owned affiliate, Akcea Therapeutics, Inc., which we formed in December 2014. In July 2017, Akcea completed an initial public offering, or IPO. Since Akcea's IPO, our ownership has ranged from 68 percent to 77 percent. At December 31, 2019, our ownership was approximately 76 percent. We reflect changes in our ownership of Akcea in our financial statements in the period the change occurs. For example, we reflected an increase in our ownership when we received 6.9 million shares of Akcea common stock as payment for the sublicense fee Akcea owed us for Pfizer's license of AKCEA-ANGPTL3-L_{Rx} in the fourth quarter of 2019. Refer to the section titled "Noncontrolling Interest in Akcea" in Note 2, *Significant Accounting Policies*, for further information related to our accounting for our investment in Akcea.

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 per Share

Basic net income per share

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

The calculation of total net income attributable to our common stockholders for each year considered our net income 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 available to Ionis common stockholders for the calculation of net income per share is different than net income attributable to Ionis Pharmaceuticals, Inc. common stockholders in our consolidated statements of operations for each year.

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

Year Ended December 31, 2019	Weighted Average Shares Owned in Akcea	Akcea's Net Income Per Share	Ionis' Portion of Akcea's Net Income
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	Ionis' Portion of Akcea's Net Loss
Common shares	59,812	$ (2.74)	$ (163,938)
Akcea's net loss attributable to our ownership			$ (163,938)
Ionis' stand-alone net income			440,806
Net income available to Ionis common stockholders			$ 276,868
Weighted average shares outstanding			132,320
Basic net income per share			$ 2.09

We calculated our basic net income per share for 2017 as follows (in thousands, except per share amounts):

Year Ended December 31, 2017	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	20,669	$ (3.08)	$ (63,638)
Preferred shares	15,748	(1.80)	(28,346)
Akcea's net loss attributable to our ownership			$ (91,984)
Ionis' stand-alone net income			110,776
Net income available to Ionis common stockholders			$ 18,792
Weighted average shares outstanding			124,016
Basic net income per share			$ 0.15

Prior to Akcea's IPO in July 2017, we owned Akcea series A convertible preferred stock, which included a six percent cumulative dividend. Upon completion of Akcea's IPO in July 2017, our preferred stock was converted into common stock on a 1:1 basis. The preferred stock dividend was not paid at the IPO because the IPO was not a liquidation event or a change in control. During 2017, Akcea used a two-class method to compute its net loss per share because it had both common and preferred shares outstanding during the periods. The two-class method required Akcea to calculate its net loss per share for each class of stock by dividing total distributable losses applicable to preferred and common stock, including the six percent cumulative dividend contractually due to series A convertible preferred shareholders, by the weighted-average of preferred and common shares outstanding during the requisite period. Since Akcea used the two-class method, accounting rules required us to include our portion of Akcea's net loss per share for both Akcea's common and preferred shares that we owned in our calculation of basic and diluted net income per share for the year ended December 31, 2017.

Diluted net income per share

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	$ 2.12
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 Employee Stock Purchase Plan	—	18	
Income available to Ionis common stockholders, plus assumed conversions	$ 296,563	142,872	$ 2.08

Year Ended December 31, 2018	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 276,868	132,320	$ 2.09
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 Employee Stock Purchase Plan	—	6	
Income available to Ionis common stockholders, plus assumed conversions	$ 276,868	134,056	$ 2.07

Year Ended December 31, 2017	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 18,792	124,016	$ 0.15
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,619	
Shares issuable upon restricted stock award issuance	—	459	
Shares issuable related to our Employee Stock Purchase Plan	—	4	
Income available to Ionis common stockholders, plus assumed conversions	$ 18,792	126,098	$ 0.15

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 future sales milestone payments and royalties we earn under our 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, prior to the third quarter of 2019 we distributed TEGSEDI through a non-exclusive distribution model with a 3PL that took title to TEGSEDI. The 3PL was our sole customer in Europe. The 3PL in Europe then distributed TEGSEDI to hospitals and pharmacies. In the third quarter of 2019, we entered into a distribution arrangement with a 3PL and began to sell both TEGSEDI and WAYLIVRA directly to hospitals and pharmacies in Europe.

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.

Our collaboration agreements are detailed 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 is probable.

2. Identify the performance obligations

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

Often times 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. These items are contingent upon future events that may not occur. 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 are usually based on scientific progress. For example, in the fourth quarter of 2019, we earned a $10 million milestone payment from AstraZeneca when AstraZeneca initiated a Phase 1 trial for ION839. We did not consider the milestone payments probable until AstraZeneca achieved the milestone event because the initiation of the Phase 1 trial was a contingent event that was not within our control. We recognized the milestone payments 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 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 on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- 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.

We do not reallocate the transaction price after the start of an agreement to reflect subsequent changes in stand-alone selling prices.

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. For example, in the third quarter of 2019, we updated our estimate of the total effort we expected to expend to satisfy our performance obligation under our 2013 Strategic Neurology collaboration with Biogen. As of September 30, 2019, we had completed a significant portion of the research and development services. We expect to complete the remainder of our services in 2020. As a result of our change in estimate, in the third quarter of 2019, we recorded a cumulative catch up adjustment of $16.5 million to decrease revenue. Refer to Note 7, *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 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, co-pay assistance 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 an accrued liability on our consolidated balance sheet for the chargebacks related to product sales to our U.S. customer during the reporting period.

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 a value-based agreement with one of our commercial payer's. We record these rebates as an accrual 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 EU customers 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 selling, general and administration, or 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. Our EU customers only take title to the product after they receive an order from a hospital or pharmacy and therefore they do not maintain excess inventory levels of our products. Accordingly, we have limited return risk in the EU and we do not estimate returns in the EU.

Other incentives: In the U.S., we estimate reserves for other incentives including co-payment assistance we provide to patients with commercial insurance who have coverage and reside in states that allow co-payment assistance. We record a reserve for the amount we estimate we will pay for co-payment assistance. We base our reserve on the number of estimated claims and our estimate of the cost per claim related to product sales that we have recognized as revenue. We record our other incentive reserve estimates 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.

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 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 2019, we achieved two $7.5 million milestone payments from Biogen when we advanced two new targets for undisclosed neurological diseases under our 2018 strategic neurology collaboration. We added these payments to the transaction price and allocated it to our R&D services performance obligation. We are recognizing revenue related to these milestone payments 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 fourth quarter of 2019, we recognized a $10 million milestone payment when Biogen advanced the development candidate for an undisclosed target under our 2012 neurology collaboration agreement. We concluded that the milestone payment was not related to our R&D services performance obligation. Therefore, we recognized the milestone payment in full in the fourth quarter of 2019.

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 2019, we earned a $45 million license fee when Biogen licensed IONIS-MAPT$_{Rx}$ from us. We also recognized $246 million of license fee revenue related to Akcea's license of AKCEA-ANGPTL3-L$_{Rx}$ to Pfizer in the fourth quarter of 2019.

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 second quarter of 2019, we earned a $20 million sublicense fee when Alnylam Pharmaceuticals sublicensed our technology to Regeneron Pharmaceuticals.

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 at their 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 7, *Collaborative Arrangements and Licensing Agreements*, for further discussion of our accounting treatment for our 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 contract 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, 2019 and 2018, we recognized $159.5 million and $105.3 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. We previously expensed $0.7 million and $0.1 million of costs to produce our products related to the product sales revenue we recognized in 2019 and 2018, respectively.

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, 2019, 2018 and 2017, research and development expenses were $461.5 million, $411.9 million and $372.5 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, 2019, 2018 and 2017, research and development costs of approximately $83.2 million, $58.7 million and $59.5 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, 2019.

The cost of our patents capitalized on our consolidated balance sheet at December 31, 2019 and 2018 was $34.0 million and $32.7 million, respectively. Accumulated amortization related to patents was $8.3 million and $8.7 million at December 31, 2019 and 2018, respectively.

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

Year Ending December 31,	Amortization (in millions)
2020	$ 1.8
2021	$ 1.8
2022	$ 1.7
2023	$ 1.6
2024	$ 1.4

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 2019, 2018 and 2017, patent expenses were $4.2 million, $2.6 million and $2.1 million, respectively, and included non-cash charges related to the write-down of our patent costs to their estimated net realizable values of $2.2 million, $0.8 million and $0.4 million, respectively.

Accrued Liabilities

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

	December 31,	
	2019	2018
Clinical expenses	$ 24,461	$ 22,125
In-licensing expenses	10,289	12,298
Other miscellaneous expenses	32,019	13,080
Total accrued liabilities	$ 66,769	$ 47,503

Noncontrolling Interest in Akcea Therapeutics, Inc.

Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea. Since Akcea's IPO, our ownership has ranged from 68 percent to 77 percent. At December 31, 2019, our ownership was approximately 76 percent. We reflect changes in our ownership percentage in our financial statements as an adjustment to noncontrolling interest in the period the change occurs. During 2019, we received the following additional shares of Akcea common stock:

- 2.8 million shares in the first quarter of 2019 as payment for the sublicense fee Akcea owed us for Novartis's license of AKCEA-APO(a)-L_{Rx}, and;
- 6.9 million shares in the fourth quarter of 2019 as payment for the sublicense fee Akcea owed us for Pfizer's license of AKCEA-ANGPTL3-L_{Rx}.

The shares third parties own represent an interest in Akcea's equity that we do control. However, as we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our consolidated financial statements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on the statement of operations and a separate line within stockholders' equity in our consolidated balance sheet. In addition, we record a noncontrolling interest adjustment to account for the stock options Akcea grants, which if exercised, will dilute our ownership in Akcea. This adjustment is 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.

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. 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, 2019, 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 five privately-held companies, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd.

In January 2018, we adopted the amended accounting guidance related to the recognition, measurement, presentation, and disclosure of certain financial instruments. The amended guidance requires us to measure and record our equity investments at fair value. Additionally, the amended accounting guidance requires us to recognize the changes in fair value in our consolidated statement of operations, instead of through accumulated other comprehensive income. Prior to 2018, we accounted for our equity investments in privately held companies under the cost method of accounting. Under the amended guidance 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. Our adoption of this guidance did not have an impact on our results.

Inventory Valuation

We reflect our inventory on our consolidated balance sheet at the lower of cost or market 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, 2019, 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 year ended December 31, 2019. We did not record any inventory write-offs for the years ended December 31, 2018 or 2017.

Our inventory consisted of the following (in thousands):

	December 31,	
	2019	2018
Raw materials:		
Raw materials- clinical	$ 9,363	$ 8,497
Raw materials- commercial	6,520	—
Total raw materials	15,883	8,497
Work in process	2,039	—
Finished goods	258	85
Total inventory	$ 18,180	$ 8,582

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):

	Estimated Useful Lives (in years)	December 31, 2019	December 31, 2018
Computer software, laboratory, manufacturing and other equipment	3 to 10	$ 60,965	$ 53,496
Building, building improvements and building systems	15 to 40	119,830	97,528
Land improvements	20	2,853	2,853
Leasehold improvements	5 to 15	13,600	18,981
Furniture and fixtures	5 to 10	7,354	6,283
		204,602	179,141
Less accumulated depreciation		(74,013)	(61,474)
		130,589	117,667
Land		23,062	14,493
Total		$ 153,651	$ 132,160

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

Topic 842 Adoption

In February 2016, the Financial Accounting Standards Board, or FASB, issued amended accounting guidance related to lease accounting. This guidance supersedes the lease requirements we previously followed in Accounting Standards Codification, or ASC, Topic 840, *Leases*, or Topic 840, and created a new lease accounting standard, Topic 842, *Leases*, or Topic 842. Under Topic 842, an entity will record on its balance sheet all leases with a term longer than one year. Further, an entity will record a liability with a value equal to the present value of payments it will make over the life of the lease (lease liability) and an asset representing the underlying leased asset (right-of-use asset). The new accounting guidance requires entities to determine if its leases are operating or financing leases. Entities will recognize expense for operating leases on a straight-line basis as an operating expense. If an entity determines a lease is a financing lease, it will record both interest and amortization expense and generally the expense will be higher in the earlier periods of the lease. We adopted Topic 842 on January 1, 2019 and adjusted our opening balance sheet on that date for our right-of-use operating lease assets and operating lease liabilities. At adoption, we recorded $13.5 million in right-of-use operating lease assets and $18.5 million in operating lease liabilities, of which we classified $2 million as a current liability. We adopted Topic 842 using the available practical expedients permitted under the transition guidance within the new standard, which among other things, allowed us to carry forward the historical lease classification of those leases we had in place as of January 1, 2019. The adoption did not have an impact on our consolidated statement of operations.

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 determined the lease term at the inception of the 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.

As our current leases do not provide an interest rate implicit in the lease, we used our or Akcea's incremental borrowing rate, based on the information available on the date we adopted Topic 842 or as of the lease inception date in determining the present value of future payments. Our right-of-use operating lease asset also includes any lease payments we made and excludes any tenant improvement allowances we received. 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 $2.2 million, $0.8 million and $0.8 million for the years ended December 31, 2019, 2018 and 2017, respectively, related primarily to the write-down of intangible assets.

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, restricted stock units, or 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.

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.

See Note 4, *Stockholders' Equity,* for additional information regarding our stock-based compensation plans.

Accumulated Other Comprehensive Loss

Accumulated other comprehensive loss is primarily comprised of unrealized gains and losses on investments, net of taxes and adjustments we made to reclassify realized gains and losses on investments from other accumulated comprehensive loss to our Consolidated Statement of Operations. The following table summarizes changes in accumulated other comprehensive loss for the years ended December 31, 2019, 2018 and 2017 (in thousands):

	Year Ended December 31,		
	2019	2018	2017
Beginning balance accumulated other comprehensive loss	$ (32,016)	$ (31,759)	$ (30,358)
Unrealized gains (losses) on securities, net of tax (1)	6,633	(280)	(960)
Amounts reclassified from accumulated other comprehensive loss	—	—	(374)
Currency translation adjustment	93	23	(67)
Net other comprehensive loss for the period	6,726	(257)	(1,401)
Ending balance accumulated other comprehensive loss	$ (25,290)	$ (32,016)	$ (31,759)

(1) A tax benefit of $1.4 million and $0.3 million was included in other comprehensive loss for the years ended December 31, 2019 and 2018, respectively. There was no tax benefit or expense for other comprehensive loss for the year ended December 31, 2017.

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 recently issued non-convertible debt instruments. 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*.

Segment Information

We have two operating segments, our Ionis Core segment and Akcea Therapeutics, our majority-owned affiliate. Akcea is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with serious and rare diseases. We provide 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 reviews to assess operating performance and to make operating decisions. We allocate a portion of Ionis' development, R&D support and general and administrative expenses to Akcea for work Ionis performs on behalf of Akcea and we bill 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 the majority 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, 2019 and 2018 that we regularly measure and carry at fair value. At December 31, 2019, a portion of our ProQR investment was subject to trading restrictions through 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. At December 31, 2018, our ProQR investment was subject to trading restrictions through the fourth quarter of 2019, as a result we included a lack of marketability discount in valuing this investment, which is a Level 3 input. The 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, 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 (2)	1,102,568	—	1,102,568	—
Debt securities issued by U.S. government agencies (3)	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	$ 2,258,985	$ 782,100	$ 1,472,379	$ 4,506

	At December 31, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 146,281	$ 146,281	$ —	$ —
Corporate debt securities (6)	1,252,960	—	1,252,960	—
Debt securities issued by U.S. government agencies (4)	276,612	—	276,612	—
Debt securities issued by the U.S. Treasury (7)	260,154	260,154	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (4)	79,942	—	79,942	—
Investment in ProQR Therapeutics N.V. (5)	1,349	—	—	1,349
Total	$ 2,017,298	$ 406,435	$ 1,609,514	$ 1,349

(1) Included in cash and cash equivalents on our consolidated balance sheet.

(2) $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.

(3) $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.

(4) Included in short-term investments.

(5) Included in other current assets on our consolidated balance sheet.

(6) $50.2 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) $14.2 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.

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cuts and Jobs Act of 2017, or the Tax Act. The Tax Act created a new requirement on global intangible low-taxed income, or GILTI, earned by foreign subsidiaries for tax years beginning on or after January 1, 2018. The GILTI provisions require foreign subsidiary earnings in excess of an allowable return on the foreign subsidiary's assets to be included in our U.S. income tax return. Under U.S. GAAP, we are permitted to make an accounting policy election to either treat taxes due on future inclusions in U.S. taxable income related to GILTI as a current-period expense when incurred or to factor such amounts into our measurement of deferred taxes. We have made the election to account for GILTI as a component of current taxes incurred rather than as a component of deferred taxes.

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 the new guidance on January 1, 2020. We do not expect this guidance will 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. We do not expect this guidance will have an impact on our consolidated financial statements.

In August 2018, the FASB updated its disclosure requirements related to Level 1, 2 and 3 fair value measurements. The update included deletion and modification of certain disclosure requirements and additional disclosure related to Level 3 measurements. The guidance is effective for fiscal years beginning after December 31, 2019 and early adoption is permitted. We adopted this updated guidance on January 1, 2019 and it did not have a significant impact on our disclosures.

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 will implement 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 will apply 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 will 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 will not recognize revenue for the transaction*

We adopted this new guidance on January 1, 2020. We do not expect this guidance will have a significant impact on our consolidated financial statements.

In December 2019, the FASB issued guidance to simplify the accounting for income taxes. The update includes removing several exceptions under the existing guidance and includes several simplification updates, none of which apply to our current accounting for income taxes. The guidance is effective for fiscal years beginning after December 15, 2020 and early adoption is permitted. We adopted this updated guidance in the fourth quarter of 2019 and it did not have an impact on our consolidated financial statements or disclosures.

2. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2019:

One year or less	70%
After one year but within two years	20%
After two years but within three and a half years	10%
Total	100%

As illustrated above, at December 31, 2019, 90 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, 2019, we had an ownership interest of less than 20 percent in five private companies and two public companies with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., 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, 2019	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
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

December 31, 2018	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 956,879	$ 13	$ (1,858)	$ 955,034
Debt securities issued by U.S. government agencies	168,839	3	(104)	168,738
Debt securities issued by the U.S. Treasury	244,640	15	(77)	244,578
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	63,572	—	(323)	63,249
Total securities with a maturity of one year or less	1,433,930	31	(2,362)	1,431,599
Corporate debt securities	299,018	194	(1,286)	297,926
Debt securities issued by U.S. government agencies	107,789	194	(109)	107,874
Debt securities issued by the U.S. Treasury	15,600	—	(24)	15,576
Debt securities issued by states of the U.S. and political subdivisions of the states	16,980	—	(287)	16,693
Total securities with a maturity of more than one year	439,387	388	(1,706)	438,069
Total available-for-sale securities	$ 1,873,317	$ 419	$ (4,068)	$ 1,869,668
Equity securities:				
Total equity securities included in other current assets (3)	$ 1,212	$ 137	$ —	$ 1,349
Total available-for-sale and equity securities	$ 1,874,529	$ 556	$ (4,068)	$ 1,871,017

(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 investment in ProQR, which is a public company. We recognize our public company equity securities at fair value.

(4) Our equity securities included in deposits and other assets consisted of our investment in Empirico, which is a private company. 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.

Investments we consider to be temporarily impaired at December 31, 2019 are as follows (in thousands):

	Number of Investments	Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
		Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	49	$ 131,702	$ (75)	$ 11,840	$ (11)	$ 143,542	$ (86)
Debt securities issued by U.S. government agencies	43	149,731	(136)	37,041	(24)	186,772	(160)
Debt securities issued by the U.S. Treasury	10	84,270	(39)	—	—	84,270	(39)
Debt securities issued by states of the U.S. and political subdivisions of the states	11	10,241	(5)	10,303	(6)	20,544	(11)
Total temporarily impaired securities	113	$ 375,944	$ (255)	$ 59,184	$ (41)	$ 435,128	$ (296)

We believe that the decline in value of our debt securities is temporary and 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 these securities to maturity. Therefore, we anticipate full recovery of our debt securities' amortized cost basis at maturity.

3. Long-Term Obligations and Commitments

The carrying value of our long-term obligations was as follows (in thousands):

	December 31,	
	2019	2018
0.125 percent convertible senior notes	$ 434,711	$ —
1 percent convertible senior notes	275,333	568,215
Long-term mortgage debt	59,913	59,842
Principal balance of fixed rate note with Morgan Stanley (1)	—	12,500
Leases and other obligations	17,569	6,163
Total	$ 787,526	$ 646,720
Less: current portion	(2,026)	(13,749)
Total Long-Term Obligations	$ 785,500	$ 632,971

(1) Our $12.5 million fixed rate note with Morgan Stanley was included in our current portion of long-term obligations on our consolidated balance sheet at December 31, 2018. We paid off our fixed rate note in the third quarter of 2019.

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, 2019, we had the following 0.125% Notes outstanding (amounts in millions except price per share data):

	0.125% Notes
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, 2019:

	0.125% Notes
Fair value of outstanding notes	$ 558.7
Principal amount of convertible notes outstanding	$ 548.8
Unamortized portion of debt discount	$ 105.2
Long-term debt	$ 434.7
Carrying value of equity component	$ 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.

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 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, 2019, we had the following 1% Notes outstanding (amounts in millions except price per share data):

	1% Notes
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, 2019:

	December 31,	
	2019	2018
Fair value of outstanding notes	$ 354.8	$ 725.0
Principal amount of convertible notes outstanding	$ 309.9	$ 685.5
Unamortized portion of debt discount	$ 32.8	$ 110.8
Long-term debt	$ 275.3	$ 568.2
Carrying value of equity component	$ 33.5	$ 219.0

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:

	1% Notes	0.125% Notes
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, 2019, 2018 and 2017 included $39.3 million, $35.2 million and $32.5 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.

As a result of the purchase, we extinguished the financing liability we had previously recorded on our balance sheet for our primary R&D facility. The difference between the purchase price of our primary R&D facility and the carrying value of our financing liability at the time of the purchase was $7.7 million. We recognized this amount as a non-cash loss on extinguishment of financing liability for leased facility in our consolidated results of operations in the third quarter of 2017. We previously accounted for the lease of our manufacturing facility as an operating lease. We capitalized the purchase price of the manufacturing facility as a fixed asset in the third quarter of 2017.

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2019 are as follows (in thousands):

2020	$ 6,260
2021	316,114
2022	3,495
2023	4,180
2024	553,006
Thereafter	64,429
Subtotal	$ 947,484
Less: current portion	(2,026)
Less: fixed and determinable interest	(28,014)
Less: unamortized portion of debt discount	(137,975)
Plus: lease liabilities	17,235
Total	$ 796,704

Operating Leases

Ionis 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 with an initial term ending in June 2021 and an option to extend the lease for up to two five-year periods.

We also lease additional office spaces. We sublease a portion of one of these spaces to Akcea. We lease these spaces under non-cancelable operating leases with initial terms ending in 2023 with options to extend the leases for one five-year period. The sublease with Akcea is eliminated in our consolidated financial statements.

Akcea Lease

Akcea entered into an operating lease agreement for office space located in Boston, Massachusetts for its new corporate headquarters in the second quarter of 2018. The lease commencement date was in August 2018 and Akcea took occupancy in September 2018. Akcea is 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, Akcea received a three-month free rent period, which commenced on August 15, 2018, and a tenant improvement allowance up to $3.8 million. Akcea 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 Akcea meets 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.

Amounts related to our operating leases were as follows (dollar amounts in millions):

	At December 31, 2019
Right-of-use operating lease assets (1)	$ 12.6
Operating lease liabilities (2)	$ 17.2
Weighted average remaining lease term	8.1 years
Weighted average discount rate	7.6%

(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 year ended December 31, 2019, we paid $3.9 million of lease payments, which was included in operating activities in our consolidated statement of cash flows.

As of December 31, 2019, the future payments for our operating lease liabilities are as follows (in thousands):

	Operating Leases
Year ending December 31,	$
2020	3,285
2021	3,022
2022	2,781
2023	2,520
2024	2,396
Thereafter	9,465
Total minimum lease payments	23,469
Less:	
Imputed interest	(6,234)
Total operating lease liabilities	$ 17,235

Rent expense was $3.6 million, $2.6 million and $1.7 million for the years ended December 31, 2019, 2018 and 2017, 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, 2019, 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, 2019.

Common Stock

At December 31, 2019 and 2018, we had 300 million shares of common stock authorized, of which 140.3 million and 137.9 million were issued and outstanding, respectively. As of December 31, 2019, total common shares reserved for future issuance were 26.2 million.

During the years ended December 31, 2019, 2018 and 2017, we issued 3.1 million, 1.5 million and 1.7 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 $119.7 million, $27.9 million and $22.9 million in 2019, 2018 and 2017, respectively.

Share Repurchase Program

In September 2019, our board of directors approved an initial share repurchase program of up to $125 million of our common stock. Our stock repurchase program has no expiration date. Through December 31, 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 $90.6 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, 2019, a total of 0.1 million options were outstanding, of which options to purchase 0.1 million shares were exercisable, and 0.04 million 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 2021. 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. Under the 2011 Plan, stock options cannot vest in a period of less than two years and restricted stock unit awards cannot vest in a period of less than three years. 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, 2019, a total of 10.0 million options were outstanding, of which 5.4 million were exercisable, 1.7 million restricted stock unit awards were outstanding, and 7.4 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 issue to Dr. Stanley T. Crooke in his former role as chief executive officer and 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.

Corporate Transactions and Change in Control under 2011 Plan

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 Plan:

- 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 Non-Employee Directors Stock Option Plan to increase the total number of shares reserved for issuance. We increased the shares available under our 2002 Non-Employee Directors Stock Option Plan from 1.2 million to 2.0 million. Options under this plan expire 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2019, a total of 0.9 million options were outstanding, of which 0.5 million were exercisable, 0.1 million restricted stock unit awards were outstanding, and 0.1 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, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 3.7 million shares authorized under the plan as of December 31, 2019. 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 2019, employees purchased and we issued to employees 0.05 million shares under the ESPP at a weighted average price of $40.95 per share. At December 31, 2019, 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, 2019 (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, 2018	11,311	$ 47.85		
Granted	2,543	$ 56.19		
Exercised	(2,617)	$ 40.48		
Cancelled/forfeited/expired	(236)	$ 50.11		
Outstanding at December 31, 2019	11,001	$ 51.48	4.41	$ 104,029
Exercisable at December 31, 2019	6,004	$ 50.95	3.34	$ 59,780

The weighted-average estimated fair values of options granted were $28.76, $25.49 and $25.42 for the years ended December 31, 2019, 2018 and 2017, respectively. The total intrinsic value of options exercised during the years ended December 31, 2019, 2018 and 2017 were $83.8 million, $34.8 million and $49.5 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $105.9 million, $18.9 million and $21.2 million for the years ended December 31, 2019, 2018 and 2017, respectively. For the year ended December 31, 2019, the weighted-average fair value of options exercised was $72.52. As of December 31, 2019, total unrecognized compensation cost related to non-vested stock options was $97.5 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.3 years.

Restricted Stock Unit Activity

The following table summarizes the RSU activity for the year ended December 31, 2019 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2018	1,246	$ 50.20
Granted	1,114	$ 60.23
Vested	(422)	$ 51.36
Cancelled/forfeited	(72)	$ 53.39
Non-vested at December 31, 2019	1,866	$ 55.80

For the years ended December 31, 2019, 2018 and 2017, the weighted-average grant date fair value of RSUs granted was $60.23, $51.06 and $48.88 per RSU, respectively. As of December 31, 2019, total unrecognized compensation cost related to RSUs was $56.5 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.5 years.

Stock-based Compensation Expense and Valuation Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2019, 2018 and 2017 (in thousands), which was allocated as follows and includes $37.1 million, $44.3 million and $17.5 million of stock-based compensation expense for Akcea employees in 2019, 2018 and 2017, respectively:

	Year Ended December 31,		
	2019	2018	2017
Cost of products sold	$ 438	$ 160	$ —
Research, development and patent	95,348	76,557	64,521
Selling, general and administrative	50,788	54,595	21,454
Total	$ 146,574	$ 131,312	$ 85,975

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. In the fourth quarter of 2019, Akcea adjusted its stock-based compensation expense for an additional executive officer who will terminate his employment in April 2020.

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, 2019, 2018 and 2017, we used the following weighted-average assumptions in our Black-Scholes calculations:

Ionis Employee Stock Options:

	December 31,		
	2019	2018	2017
Risk-free interest rate	2.3%	2.4%	1.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	60.3%	63.0%	65.9%
Expected life	4.8 years	4.6 years	4.5 years

Ionis Board of Director Stock Options:

	December 31,		
	2019	2018	2017
Risk-free interest rate	1.9%	2.8%	2.2%
Dividend yield	0.0%	0.0%	0.0%
Volatility	60.7%	61.5%	61.2%
Expected life	6.6 years	6.6 years	6.6 years

Ionis ESPP:

	December 31,		
	2019	2018	2017
Risk-free interest rate	2.4%	1.8%	0.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	45.6%	47.3%	59.9%
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 has its own stock plan under which it grants options and RSUs and under which it derives its stock-based compensation expense. The following are the weighted-average Black-Scholes assumptions Akcea used under its plan for the years ended December 31, 2019, 2018 and 2017:

Akcea Employee Stock Options:

	December 31,		
	2019	**2018**	**2017**
Risk-free interest rate	2.2%	2.8%	1.9%
Dividend yield	0.0%	0.0%	0.0%
Volatility	75.4%	77.1%	79.5%
Expected life	6.09 years	6.08 years	6.06 years

Akcea Board of Director Stock Options:

	December 31,		
	2019	**2018**	**2017**
Risk-free interest rate	1.8%	2.9%	1.9%
Dividend yield	0.0%	0.0%	0.0%
Volatility	73.8%	78.2%	79.4%
Expected life	6.25 years	6.42 years	6.25 years

Akcea ESPP:

	December 31,		
	2019	**2018**	**2017**
Risk-free interest rate	2.4%	1.9%	1.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	60.0%	64.2%	73.3%
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 does not have sufficient history to estimate the volatility of its common stock, Akcea calculates its expected volatility based on a blend of its historical volatility and reported data from selected publicly traded peer companies for which historical information is available. Akcea plans to continue to use this blend to calculate its volatility until the historical volatility of its common stock is sufficient to measure expected volatility for future option grants.

Expected Life. Since Akcea does not have sufficient historical information, it uses the simplified method for estimating its expected term. Under the simplified method Akcea calculates its expected term as the average time-to-vesting and the contractual life of the options. As Akcea gains additional historical information, it will transition to calculating its expected term based on its exercise patterns.

5. Income Taxes

Income (loss) before income taxes is comprised of (in thousands):

	Year Ended December 31,		
	2019	2018	2017
United States	$ 344,280	$ (69,576)	$ (5,289)
Foreign	2,489	(6,580)	(11,474)
Income (loss) before income taxes	$ 346,769	$ (76,156)	$ (16,763)

Our income tax expense (benefit) was as follows (in thousands):

	Year Ended December 31,		
	2019	2018	2017
Current:			
Federal	$ 35,861	$ 438	$ (7,460)
State	14,329	(1,442)	1,246
Foreign	413	374	234
Total current income tax expense (benefit)	50,603	(630)	(5,980)
Deferred:			
Federal	(7,096)	(290,511)	—
State	—	—	—
Total deferred income tax benefit	(7,096)	(290,511)	—
Total income tax expense (benefit)	$ 43,507	$ (291,141)	$ (5,980)

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,					
	2019		2018		2017	
Pre-tax income (loss)	$ 346,769		$ (76,156)		$ (16,763)	
Statutory rate	72,822	21.0%	(15,993)	21.0%	(5,867)	35.0%
State income tax net of federal benefit	49,119	14.2%	(2,202)	2.9%	820	(4.9)%
Foreign	340	0.1%	1,735	(2.3)%	4,299	(25.6)%
Net change in valuation allowance	(37,765)	(10.9)%	(277,924)	364.9%	(86,296)	514.8%
Net operating loss expiration	—	0.0%	8,864	(11.6)%	3,987	(23.8)%
TEGSEDI licensing gain	—	0.0%	59,583	(78.2)%	—	0.0%
Impact from outside basis differences	(16,344)	(4.7)%	—	0.0%	—	0.0%
Tax credits	(22,296)	(6.4)%	(73,362)	96.3%	(32,769)	195.5%
Deferred tax true-up	646	0.2%	9,947	(13.1)%	4,848	(28.9)%
Tax rate change	1,811	0.5%	(1,808)	2.4%	114,832	(685.0)%
Non-deductible compensation	3,361	1.0%	3,154	(4.1)%	1,575	(9.4)%
Other non-deductible items	329	0.1%	(569)	0.7%	2,548	(15.2)%
Akcea deconsolidation adjustment at IPO	—	0.0%	—	0.0%	469	(2.8)%
Stock-based compensation	(4,837)	(1.4)%	(4,199)	5.5%	(14,337)	85.5%
Foreign-derived intangible income benefit	(2,071)	(0.6)%	—	0.0%	—	0.0%
Other	(1,608)	(0.5)%	1,633	(2.1)%	(89)	0.5%
Effective rate	$ 43,507	12.6%	$ (291,141)	382.3%	$ (5,980)	35.7%

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, 2019 and 2018 are as follows (in thousands):

	Year Ended December 31,	
	2019	2018
Deferred Tax Assets:		
Net operating loss carryovers	$ 20,191	$ 89,717
R&D credits	210,455	313,652
Deferred revenue	127,763	27,381
Stock-based compensation	65,703	61,027
Intangible and capital assets	77,861	49,007
Other	12,510	8,275
Total deferred tax assets	$ 514,483	$ 549,059
Deferred Tax Liabilities:		
Convertible debt	$ (6,110)	$ (24,018)
Fixed assets	(1,958)	—
Other	(3,884)	—
Net deferred tax asset	$ 502,531	$ 525,041
Valuation allowance	(196,974)	(234,245)
Total net deferred tax assets and liabilities	$ 305,557	$ 290,796

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.

We have historically recorded a valuation allowance against all our net deferred tax assets due to cumulative financial statement losses. However, in the fourth quarter of 2018, we reversed the valuation allowance previously recorded against Ionis' stand-alone U.S. federal net deferred tax assets, resulting in a one-time non-cash tax benefit of $332.1 million. We reversed the valuation allowance in 2018 as we expected to generate U.S. pre-tax income on an Ionis standalone basis in future periods at a level that would result in us fully utilizing our U.S. federal net operating loss carryforwards and our Research and Development and Orphan Drug tax credit carryforwards. We utilized a significant portion of these carryforwards in 2019 to partially offset our estimated federal tax liability for the year.

Our valuation allowance decreased by $37.3 million from December 31, 2018 to December 31, 2019. The decrease relates primarily to the current year utilization of a portion of our net deferred state tax assets, primarily California net operating loss carryovers, that had been fully reserved by the valuation allowance.

We continue to maintain a full valuation allowance of $197.0 million against all of Akcea's net deferred tax assets and the net state deferred tax assets of Ionis at December 31, 2019 due to uncertainties related to our ability to realize the tax benefits associated with these assets.

We generated combined state taxable income and recognized a combined state tax liability in 2019. We utilized Ionis' state deferred tax assets, primarily California net operating loss carry forwards, to reduce our combined state tax liability for the year by $59.1 million, which resulted in a corresponding reduction to our combined state valuation allowance. We have historically generated combined state net operating losses due primarily to Akcea's net operating losses. However, Akcea generated net income in 2019. This was due to an increase in their research and development and license revenue, primarily related to non-recurring transactions in the first and fourth quarter from Novartis' exercise of its option to license AKCEA-APO(a)-L_{Rx} and Pfizer's license of AKCEA-ANGPTL3-L_{Rx}, respectively. Although Akcea generated net income in 2019, given their history of losses, there can be no assurance that they will achieve profitability in future periods. We expect Akcea to incur additional operating losses for the foreseeable future and therefore we continue to maintain a full valuation allowance against our remaining net deferred state tax assets.

At December 31, 2019, we had federal and state, primarily California, tax net operating loss carryforwards of $99.5 million and $117.9 million, respectively. Our federal tax loss carryforwards are available indefinitely. Our California tax loss carryforwards will begin to expire in 2033. At December 31, 2019, we also had federal and California research and development tax credit carryforwards of $198.8 million and $74.1 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.

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cuts and Jobs Act of 2017, or the Tax Act. The Tax Act made broad and complex changes to the U.S. tax code, including, but not limited to, reducing the U.S. federal corporate income tax rate to 21 percent, imposing a mandatory one-time transition tax on certain unrepatriated earnings of foreign subsidiaries subjecting certain foreign earnings to U.S. taxation through base erosion anti-abuse tax, or BEAT, and global intangible low-taxed income, or GILTI, eliminating the corporate alternative minimum tax, or AMT, and changing how existing AMT credits can be realized. We were required to recognize the tax effect of the tax law changes in the year of enactment. Our accounting for the elements of the Tax Act is complete. We have made an accounting policy election to treat taxes due on the GILTI inclusion as a current period expense.

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):

	Year Ended December 31,		
	2019	2018	2017
Beginning balance of unrecognized tax benefits	$ 68,301	$ 78,014	$ 66,999
Decrease for prior period tax positions	(867)	(12,814)	—
Increase for prior period tax positions	736	—	1,520
Increase for current period tax positions	1,614	3,101	9,495
Ending balance of unrecognized tax benefits	$ 69,784	$ 68,301	$ 78,014

Included in the balance of unrecognized tax benefits at December 31, 2019, is $21.7 million that could impact our effective tax rate, subject to our remaining valuation allowance.

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. We did not recognize any accrued interest and penalties related to gross unrecognized tax benefits during the year ended December 31, 2019.

We are subject to taxation in the U.S. and various state and foreign jurisdictions. Our tax years for 1999 through 2018 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. In December 2017, we entered into a collaboration with Biogen to identify new antisense medicines for the treatment of SMA. We and Biogen are currently developing eight medicines to treat neurodegenerative diseases under these collaborations, including medicines 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 2019, we have received more than $2.4 billion from our Biogen collaborations, including $1 billion we received from Biogen in the second quarter of 2018 for our 2018 strategic neurology collaboration.

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. Biogen reported in January 2020 that SPINRAZA was approved in over 50 countries around the world. From inception through December 2019, we earned more than $1 billion in total revenue under our SPINRAZA collaboration, including more than $640 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 global development, regulatory and commercialization activities and costs for SPINRAZA.

We completed our performance obligations under our collaboration in 2016, including delivering the license to Biogen in July 2016. We also earned additional milestone payments subsequent to delivering the license to Biogen that we recognized in full in the period each milestone payment became probable because we did not have a performance obligation related to each milestone payment. For example, we received $90 million of milestone payments for the approval of SPINRAZA in the EU and Japan in 2017 and recognized the full amounts into revenue in the period Biogen achieved the milestone events.

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 all further 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, 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 millionfor 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 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. 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 targets. Biogen is responsible for conducting IND-enabling toxicology studies for the selected target. Biogen will have the option to license the selected target after it completes the IND-enabling toxicology study. If Biogen exercises its option to license a medicine, it will assume all further 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 inception through December 2019, we have received over $1 billion in payments under this collaboration, excluding $15 million we generated in the fourth quarter of 2019 for advancing two targets under this collaboration. We will achieve the next payment of $7.5 million if Biogen designates another target 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 2019, we have included $597 million in payments in the transaction price for our R&D services performance obligation under this collaboration, including four $7.5 million milestone payments we achieved in 2019 for advancing four targets under this collaboration. 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 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 all further global development, regulatory and commercialization responsibilities and costs for that medicine. We are currently advancing five medicines in development under this collaboration, including a medicine for Parkinson’s disease, two medicines for ALS and two medicines for undisclosed targets. In December 2018, Biogen exercised its option to license one of our ALS medicines, tofersen, and as a result Biogen is now responsible for all further 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 2019, we have received over $240 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 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 are recognizing 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 of September 30, 2019, we had completed a significant portion of the research and development services. We expect to complete the remainder of our services in 2020. As a result, we recorded a cumulative catch up adjustment of $16.5 million to decrease revenue in the third quarter of 2019. We will recognize this amount over the estimated remaining period we will perform services. From inception through December 2019, we have 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 generated in 2018 and 2019:

- 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 $8 million milestone payment when Biogen initiated a Phase 1/2 study of ION859 (IONIS-LRRK2$_{Rx}$) 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}$.

2012 Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense medicines to up to three targets 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. We are currently advancing IONIS-MAPT$_{Rx}$ for Alzheimer's disease and ION581 for Angelman syndrome under this collaboration. If Biogen exercises its option to license a medicine, it will assume all further 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 all further 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 2019, we have received $130 million in payments under this collaboration, including $45 million we earned when Biogen licensed IONIS-MAPT$_{Rx}$ and $10 million when Biogen advanced ION581, both of which occurred in the fourth quarter of 2019. We also achieved a $7.5 million milestone payment in the first quarter of 2020 when we advanced IONIS-MAPT$_{Rx}$. We will achieve the next payment of $12 million if we continue to advance IONIS-MAPT$_{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 for our IONIS-MAPT$_{Rx}$ development performance obligation based on the percentage of completion. From inception through December 2019, we have included $37.5 million in the transaction price for our IONIS-MAPT$_{Rx}$ development performance obligation. We currently estimate we will satisfy our performance obligation in September 2020. Our total transaction price for our IONIS-MAPT$_{Rx}$ development performance obligation includes the following payments we achieved in 2019 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}$ for Alzheimer's disease under this collaboration.
- 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 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 ION581. We recognized this milestone payment in full in the fourth quarter of 2019 because we do not have any performance obligations related to this milestone payment.

During the years ended December 31, 2019, 2018 and 2017, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Year Ended December 31,		
	2019	**2018**	**2017**
SPINRAZA royalties (commercial revenue)	$ 293.0	$ 237.9	$ 112.5
R&D revenue	180.6	137.1	150.6
Total revenue from our relationship with Biogen	$ 473.6	$ 375.0	$ 263.1
Percentage of total revenue	42%	63%	51%

Our consolidated balance sheet at December 31, 2019 and 2018 included deferred revenue of $525.8 million and $580.9 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

AstraZeneca

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 three medicines from us: IONIS-AZ4-2.5-L_{Rx}, a medicine we designed to treat cardiovascular disease and our first medicine that combines our Generation 2.5 and LICA technology, ION532, a medicine we designed to treat a genetically associated form of kidney disease and ION839, a medicine we designed to inhibit an undisclosed target to treat patients with nonalcoholic steatohepatitis, or NASH. AstraZeneca is responsible for all further 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 $4 billion as medicines under this collaboration advance, including up to $1.1 billion for the achievement of development milestones and up to $2.9 billion for 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. We will achieve the next payment of $10 million under this collaboration if we advance a medicine under this collaboration. From inception through December 2019, we have received over $175 million in upfront fees, license fees, milestone payments, and other payments under this collaboration, including a $10 million milestone payment we earned in the fourth quarter of 2019 when AstraZeneca initiated a Phase 1 trial for ION839.

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 August 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 2019, 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 IONIS-AZ4-2.5-L_{Rx}.
- In the fourth quarter of 2019, we earned a $10 million milestone payment when AstraZeneca initiated a Phase 1 study of ION839.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense medicines to treat cancer. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize danvatirsen for the treatment of cancer. AstraZeneca is responsible for all global development, regulatory and commercialization activities for danvatirsen. We and AstraZeneca have evaluated danvatirsen in people with head and neck cancer, advanced lymphoma and advanced metastatic hepatocellular carcinoma. AstraZeneca is evaluating danvatirsen in combination with durvalumab, AstraZeneca's PD-L1, blocking medicine, in people with head and neck cancer, metastatic bladder cancer and metastatic non-small cell lung 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 all further global development, regulatory and commercialization activities and costs for such medicine. In the fourth quarter of 2018, we added ION736 (formerly IONIS-AZ7-2.5$_{Rx}$) to our preclinical pipeline, a second medicine under our oncology collaboration.

Under the terms of this agreement, we received $31 million in upfront payments. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. If AstraZeneca successfully develops danvatirsen and ION736 under the research program, we could receive license fees and milestone payments of up to more than $450 million, including up to $152 million for the achievement of development milestones and up to $275 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any medicines resulting from these programs. From inception through December 2019, we have received over $125 million in upfront fees, milestone payments, and other payments under this oncology collaboration, including nearly $30 million in milestone payments we achieved when AstraZeneca advanced danvatirsen and ION736, in the fourth quarter of 2018. We will achieve the next payment of up to $25 million if we advance a medicine under our cancer research program with AstraZeneca.

At the commencement of this collaboration, we identified four performance obligations, three of which we completed in March 2014 and we completed the remaining R&D services performance obligation in February 2018. 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. We recognized these milestone payments in full in the fourth quarter because we do not have any performance obligations related to these milestone payments.

During the years ended December 31, 2019, 2018 and 2017, we earned the following revenue from our relationship with AstraZeneca (in millions, except percentage amounts):

	Year Ended December 31,		
	2019	**2018**	**2017**
R&D revenue	$ 28.1	$ 120.7	$ 21.6
Percentage of total revenue	3%	20%	4%

Our consolidated balance sheet at December 31, 2019 and 2018 included deferred revenue of $25.0 million and $40.1 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 2019, we have received over $185 million from our Bayer collaboration, including a $10 million milestone payment we earned in the fourth quarter of 2019 when Bayer decided it would advance IONIS-FXI-L$_{Rx}$. 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$_{Rx}$, which we delivered in May 2016, R&D services and delivery of API, both of which we completed in November 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 which we completed 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 do not have any performance obligations related to this milestone payment.

During the years ended December 31, 2019, 2018 and 2017, we earned the following revenue from our relationship with Bayer (in millions, except percentage amounts):

	Year Ended December 31,		
	2019	**2018**	**2017**
R&D revenue	$ 14.3	$ 5.0	$ 67.1
Percentage of total revenue	1%	1%	13%

Our consolidated balance sheet at December 31, 2019 and 2019 included deferred revenue of $2.4 million and $4.3 million, respectively, 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 rare and serious 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$_{Rx}$, 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, 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 2019, we have received more than $189 million in payments under this alliance with GSK, including a $25 million license fee we earned in the third quarter of 2019 when GSK licensed the HBV program. We will achieve the next payment of $15 million when GSK initiates a Phase 3 study of a medicine under this program.

We completed our R&D services performance obligations under our collaboration in March 2015. We identified a new performance obligation when we granted GSK the license of the HBV program and assignment of related intellectual property rights in the third quarter of 2019 because the license is 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, 2019, 2018 and 2017, we earned the following revenue from our relationship with GSK (in millions, except percentage amounts):

	Year Ended December 31,		
	2019	**2018**	**2017**
R&D revenue	$ 25.4	$ 1.6	$ 14.8
Percentage of total revenue	2%	0%	3%

We did not have any deferred revenue from our relationship with GSK at December 31, 2019 and 2018.

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. Janssen had the option to license medicines from us through the designation of development candidates for up to three programs. Under our collaboration, Janssen licensed ION253 in November 2017, which is currently in preclinical development. Prior Janssen's license of ION253, we were responsible for the discovery activities to identify development candidates. Under the license, Janssen is responsible for the global development, regulatory and commercial activities 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 2019, we have received over $75 million. 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 a target under this collaboration.

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 November 2017.

We identified separate performance obligation when Janssen licensed ION253 under our collaboration because the license we granted to Janssen was distinct from our other performance obligations. We recognized the $5 million license fee for ION253 in November 2017, because Janssen had full use of the licenses without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Janssen.

During the years ended December 31, 2019, 2018 and 2017, we earned the following revenue from our relationship with Janssen (in millions, except percentage amounts):

	Year Ended December 31,		
	2019	2018	2017
R&D revenue	$ 0.1	$ 6.6	$ 36.0
Percentage of total revenue	0%	1%	7%

We did not have any deferred revenue from our relationship with Janssen at December 31, 2019 and 2018.

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 antisense 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 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 2019, we have received over $145 million in upfront fees, milestone payments and license fees for advancing tominersen, including $35 million in milestone payments we earned in the first quarter of 2019 when Roche dosed the first patient in a Phase 3 study for tominersen. 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 September 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 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 geographic atrophy, or GA, the advanced stage of dry age-related macular degeneration, or 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 all further 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 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 when 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. We currently estimate we will satisfy our performance obligation in December 2022.

During the years ended December 31, 2019, 2018 and 2017, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	Year Ended December 31,		
	2019	2018	2017
R&D revenue	$ 57.0	$ 8.3	$ 55.7
Percentage of total revenue	5%	1%	11%

Our consolidated balance sheet at December 31, 2019 and 2018 included deferred revenue of $52.3 million and $72.6 million related to our relationship with Roche, respectively.

Akcea Collaborations

The following collaboration agreements relate to Akcea, our majority owned affiliate. Akcea is responsible for the development activities under these collaborations. As such, Akcea recognizes the associated revenue earned, cash received and expenses incurred in its statement of operations, which we reflect in our consolidated results. We also reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on our statement of operations and a separate line within stockholders' equity on our consolidated balance sheet.

For each of Akcea's collaborations Akcea pays us sublicense fees for payments that it receives and we recognize those fees as revenue in our Ionis Core operating segment results and Akcea recognizes the fees as R&D expense. In our consolidated results, we eliminate any sublicense revenue and expense.

Novartis

In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}.

Akcea received a $75 million upfront payment in the first quarter of 2017, of which it retained $60 million and paid us $15 million as a sublicense fee. In February 2019, Novartis licensed AKCEA-APO(a)-L_{Rx} and Akcea earned a $150 million license fee. Akcea paid us $75 million as a sublicense fee in 2.8 million shares of Akcea common stock. Novartis is responsible for conducting and funding all future development, regulatory and commercialization activities for AKCEA-APO(a)-L_{Rx}, including a global Phase 3 cardiovascular outcomes study, which Novartis initiated in December 2019. In connection with Novartis' license of AKCEA-APO(a)-L_{Rx}, Akcea and Novartis established a more definitive framework under which the companies would negotiate the co-commercialization of AKCEA-APO(a)-L_{Rx} in selected markets. Included in this framework is an option by which Novartis could solely commercialize AKCEA-APO(a)-L_{Rx} in exchange for Novartis paying Akcea increased commercial milestone payments based on sales of AKCEA-APO(a)-L_{Rx}. When Novartis decided to not exercise its option for AKCEA-APOCIII-L_{Rx}, Akcea retained rights to develop and commercial AKCEA-APOCIII-L_{Rx}.

Under the collaboration, Akcea is 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. Akcea is also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of AKCEA-APO(a)-L_{Rx}. Akcea will pay 50 percent of these license fees, milestone payments and royalties to us as sublicense fees.

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 the IPO price or our common stock at a premium if an IPO did not occur by April 2018. Under the SPA, in July 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, Akcea identified four separate performance obligations:

- R&D services for AKCEA-APO(a)-L_{Rx};
- R&D services for AKCEA-APOCIII-L_{Rx};
- API for AKCEA-APO(a)-L_{Rx}; and
- API for AKCEA-APOCIII-L_{Rx}.

Akcea determined that the R&D services for each medicine and the API for each medicine were distinct from its other performance obligations.

Akcea 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.

Akcea 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 AKCEA-APO(a)-L_{Rx};
- $40.1 million for the R&D services for AKCEA-APOCIII-L_{Rx};
- $1.5 million for the delivery of AKCEA-APO(a)-L_{Rx} API; and
- $2.8 million for the delivery of AKCEA-APOCIII-L_{Rx} API.

Akcea recognized revenue related to each of the performance obligations as follows:

- Akcea completed its R&D services performance obligation for AKCEA-APO(a)-L_{Rx} in second quarter of 2019. As such, Akcea recognized all revenue it allocated to its AKCEA-APO(a)-L_{Rx} R&D services as of the end of the second quarter of 2019;
- Akcea completed its R&D services performance obligation for AKCEA-APOCIII-L_{Rx} in the fourth quarter of 2019 because Novartis elected to terminate the strategic collaboration for AKCEA-APOCIII-L_{Rx} during the period. As a result, Akcea was not required to provide any further R&D services, as such, Akcea recognized all revenue it allocated to its AKCEA-APOCIII-L_{Rx} L_{Rx} R&D services as of the end of the fourth quarter of 2019;
- Akcea recognized the amount attributed to AKCEA-APO(a)-L_{Rx} API when Akcea delivered it to Novartis in 2017; and
- Akcea recognized the amount attributed to AKCEA-APOCIII-L_{Rx} API when Akcea delivered it to Novartis in May 2018.

Akcea recognized revenue related to the R&D services for the AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} performance obligations as Akcea performed services based on its effort to satisfy its performance obligation relative to Akcea's total effort expected to satisfy its performance obligation.

During the years ended December 31, 2019 and 2018, Akcea earned the following revenue from its relationship with Novartis (in millions, except percentage amounts):

	Year Ended December 31,		
	2019	**2018**	**2017**
R&D revenue	$ 187.4	$ 50.6	$ 43.4
Percentage of total revenue	17%	8%	8%

Our consolidated balance sheet at December 31, 2018 included deferred revenue of $28.8 million related to Akcea's relationship with Novartis. We did not have any deferred revenue from our relationship with Novartis at December 31, 2019.

Pfizer

AKCEA-ANGPTL3-L_{Rx}

In October 2019, Akcea initiated a collaboration with Pfizer for the license of AKCEA-ANGPTL3-L_{Rx}, a medicine to treat people with cardiovascular and metabolic diseases. Akcea recently completed a Phase 2 study of AKCEA-ANGPTL3-L_{Rx} in patients with elevated levels of triglycerides, or hypertriglyceridemia, type 2 diabetes and non-alcoholic fatty liver disease, or NAFLD. Pfizer is responsible for all development and regulatory activities and costs beyond those associated with this study.

Under the terms of the agreement, Akcea received a $250 million upfront payment. Akcea is 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. Akcea is also eligible to earn tiered royalties in the mid-teens to low 20 percent range on annual worldwide net sales. Akcea has retained the rights to co-commercialize AKCEA-ANGPTL3-L_{Rx} in the U.S. and certain additional markets. Akcea will achieve the next payment of $75 million when Pfizer advances AKCEA-ANGPTL3-L_{Rx}.

At the commencement of this collaboration, Akcea identified three separate performance obligations:

- License of AKCEA-ANGPTL3-L_{Rx};
- R&D services for AKCEA-ANGPTL3-L_{Rx}; and
- API for AKCEA-ANGPTL3-L_{Rx}.

Akcea determined the transaction price to be $250 million, the upfront payment it received. Akcea 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 AKCEA-ANGPTL3-L_{Rx};
- $2.2 million for the R&D services for AKCEA-ANGPTL3-L_{Rx}; and
- $2.2 million for the delivery of AKCEA-ANGPTL3-L_{Rx} API.

Akcea is recognizing revenue related to each of its performance obligations as follows:

- Akcea recognized $245.6 million for the license of AKCEA-ANGPTL3-L_{Rx} in the fourth quarter of 2019 because Akcea determined the license Akcea granted to Pfizer was distinct from its other performance obligations and Pfizer had full use of the license without any continuing involvement from Akcea.
- Akcea is recognizing revenue related to the R&D services for AKCEA-ANGPTL3-L_{Rx} as Akcea performs services based on Akcea's effort to satisfy its performance obligation relative to Akcea's total effort expected to satisfy its performance obligation. Akcea expects to satisfy its R&D services performance obligation by mid-2020.
- Akcea recognized the amount attributed to the API supply for AKCEA-ANGPTL3-L_{Rx} when it delivered it to Pfizer in the fourth quarter of 2019.

During the fourth quarter of 2019, we received 6.9 million shares of Akcea common stock for payment of the $125 million sublicense fee Akcea owed us.

During the year ended December 31, 2019, Akcea earned the following revenue from its relationship with Pfizer (in millions, except percentage amounts):

	Year Ended December 31, 2019
R&D revenue	$ 248.7
Percentage of total revenue	22%

Our consolidated balance sheet at December 31, 2019 included deferred revenue of $1.3 million related to Akcea’s relationship with Pfizer.

PTC Therapeutics

In August 2018, Akcea entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America. Under the license agreement, Akcea is eligible to receive up to $26 million in payments, including $12 million it received in the third quarter of 2018, $6 million it received in the second quarter of 2019 following European Medicines Agency, or EMA, approval of WAYLIVRA, $4 million it received in the fourth quarter of 2019 when PTC received approval for TEGSEDI in Brazil, and up to $4 million in an additional regulatory milestone payment. Akcea is 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 Akcea 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. Consistent with the agreements between Ionis and Akcea, the companies will share all payments, including royalties.

At the commencement of this collaboration, Akcea identified two performance obligations, which were the licenses Akcea granted to PTC to commercialize TEGSEDI and WAYLIVRA in Latin America in the third quarter of 2018. Akcea recognized $12 million in license fee revenue at that time because PTC had full use of both licenses without any continuing involvement from Akcea. Akcea does not have any remaining performance obligations under its collaboration with PTC. Akcea can still earn additional payments and royalties as PTC commercializes the medicines.

In the second quarter of 2019, Akcea earned a $6 million payment when WAYLIVRA was approved by the EMA. Akcea recognized this payment in full in the second quarter of 2019 because it does not have any performance obligations related to this payment. Additionally, in the fourth quarter of 2019, Akcea earned $4 million when TEGSEDI was approved in Brazil. Akcea recognized this payment in full in the fourth quarter of 2019 because it does not have any performance obligations related to this payment.

During the years ended December 31, 2019 and 2018, Akcea earned the following revenue from its relationship with PTC (in millions, except percentage amounts):

	Year Ended December 31,	
	2019	2018
Licensing and other royalty revenue (commercial revenue)	$ 10.2	$ 12.0
Percentage of total revenue	1%	2%

Our consolidated balance sheet at December 31, 2019 and 2018 did not include any deferred revenue related to Akcea’s relationship with PTC.

7. Segment Information and Concentration of Business Risk

We have two reportable segments Ionis Core and Akcea Therapeutics. At December 31, 2019, we owned approximately 76 percent of Akcea. 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 is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with serious and rare diseases. Akcea generates revenue from TEGSEDI and WAYLIVRA product sales and from its collaborations.

The following tables show our segment revenue and income (loss) from operations for 2019, 2018 and 2017 (in thousands), respectively.

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	305,608	52,425	(5,583)	352,450
R&D revenue under collaborative agreements	553,038	436,118	(219,007)	770,149
Total segment revenue	$ 858,646	$ 488,543	$ (224,590)	$ 1,122,599
Total operating expenses	$ 523,207	$ 450,469	$ (216,960)	$ 756,716
Income (loss) from operations	$ 335,439	$ 38,074	$ (7,630)	$ 365,883

2018	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 237,930	$ —	$ —	$ 237,930
TEGSEDI product sales, net	—	2,237	—	2,237
Licensing and other royalty revenue	2,755	12,000	—	14,755
Total commercial revenue	240,685	14,237	—	254,922
R&D revenue under collaborative agreements	401,259	50,630	(107,137)	344,752
Total segment revenue	$ 641,944	$ 64,867	$ (107,137)	$ 599,674
Total operating expenses	$ 380,212	$ 295,683	$ (14,849)	$ 661,046
Income (loss) from operations	$ 261,732	$ (230,816)	$ (92,288)	$ (61,372)

2017	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 112,540	$ —	$ —	$ 112,540
Licensing and other royalty revenue	7,474	—	—	7,474
Total commercial revenue	120,014	—	—	120,014
R&D revenue under collaborative agreements	405,171	43,401	(54,407)	394,165
Total segment revenue	$ 525,185	$ 43,401	$ (54,407)	$ 514,179
Total operating expenses	$ 373,788	$ 163,871	$ (54,527)	$ 483,132
Income (loss) from operations	$ 151,397	$ (120,470)	$ 120	$ 31,047

The following table shows our total assets by segment at December 31, 2019 and 2018 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
December 31, 2019	$ 3,478,081	$ 599,250	$ (844,219)	$ 3,233,112
December 31, 2018	$ 2,975,491	$ 365,261	$ (672,968)	$ 2,667,784

Contracts receivables at December 31, 2019 and December 31, 2018 were comprised of approximately 75 percent and 99 percent for each year from one and four significant partners, respectively.

8. Employment Benefits

We have an employee 401(k) salary deferral plan, covering all employees. Employees could make contributions by withholding a percentage of their salary up to the IRS annual limit $19,000 and $25,000 in 2019 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately $6.4 million, $5.7 million and $3.0 million in matching contributions for the years ended December 31, 2019, 2018 and 2017, respectively.

9. 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.

In November 2019, a purported stockholder of Akcea filed an action in the Delaware Court of Chancery, captioned *City of Cambridge Retirement System v. Crooke, et al.*, C.A. No. 2019-0905, 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 stockholders. The plaintiff in the Delaware Action asserts that the Defendants breached their fiduciary duties in connection with the licensing transaction that Akcea and Ionis entered into regarding TEGSEDI and AKCEA-TTR-L_{Rx}. The plaintiff also asserts an unjust enrichment claim against Ionis. We and Akcea have moved to dismiss the plaintiff's complaint. We believe that the claims asserted in the Delaware Action are without merit.

10. Quarterly 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 quarterly data for the years ended December 31, 2019 and 2018 are as follows (in thousands, except per share data).

2019 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 297,214	$ 163,813	$ 167,892	$ 493,680
Operating expenses	$ 175,679	$ 182,640	$ 165,369	$ 233,028
Income (loss) from operations	$ 121,535	$ (18,827)	$ 2,523	$ 260,652
Net income (loss)	$ 90,884	$ (10,012)	$ 18,432	$ 203,957
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 84,443	$ (876)	$ 26,163	$ 184,415
Basic net income (loss) per share (1) (2)	$ 0.63	$ (0.01)	$ 0.19	$ 1.31
Diluted net income (loss) per share (1) (3)	$ 0.62	$ (0.01)	$ 0.18	$ 1.28

2018 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 144,419	$ 117,747	$ 145,395	$ 192,113
Operating expenses	$ 147,720	$ 168,028	$ 163,967	$ 181,331
Income (loss) from operations	$ (3,301)	$ (50,281)	$ (18,572)	$ 10,782
Net income (loss)	$ (10,812)	$ (56,573)	$ (20,365)	$ 302,735
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (1,420)	(40,358)	(4,559)	320,078
Basic net income (loss) per share (1) (2)	$ (0.01)	$ (0.29)	$ (0.03)	$ 2.32
Diluted net income (loss) per share (1) (3)	$ (0.01)	$ (0.29)	$ (0.03)	$ 2.21

(1) We computed net income (loss) per share independently for each of the quarters presented. Therefore, the sum of the quarterly net income (loss) per share will not necessarily equal the total for 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 quarters in 2019 and 2018 considered our net income 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 for each quarter in 2019 was calculated as follows (in thousands, except per share amounts):

Three Months Ended March 31 , 2019	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Income Per Share**	**Ionis' Portion of Akcea's Net Income**
Common shares	68,582	$ 0.35	$ 23,846
Akcea's net income attributable to our ownership			$ 23,846
Ionis' stand-alone net income			63,697
Net income available to Ionis common stockholders			$ 87,543
Weighted average shares outstanding			138,582
Basic net income per share			$ 0.63

Three Months Ended June 30 , 2019	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Loss Per Share**	**Ionis' Portion of Akcea's Net Loss**
Common shares	70,221	$ (0.40)	$ (28,244)
Akcea's net loss attributable to our ownership			$ (28,244)
Ionis' stand-alone net income			27,311
Net loss available to Ionis common stockholders			$ (933)
Weighted average shares outstanding			140,247
Basic net loss per share			$ (0.01)

Three Months Ended September 30 , 2019	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Loss Per Share**	**Ionis' Portion of Akcea's Net Loss**
Common shares	70,221	$ (0.34)	$ (23,772)
Akcea's net loss attributable to our ownership			$ (23,772)
Ionis' stand-alone net income			49,930
Net income available to Ionis common stockholders			$ 26,158
Weighted average shares outstanding			140,551
Basic net income per share			$ 0.19

Three Months Ended December 31 , 2019	**Weighted Average Shares Owned in Akcea**	**Akcea's Net Income Per Share**	**Ionis' Portion of Akcea's Net Income**
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

Our basic net income (loss) per share for each quarter in 2018 was calculated as follows (in thousands, except per share amounts):

Three Months Ended March 31 , 2018	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	45,448	$ (0.44)	$ (19,997)
Akcea's net loss attributable to our ownership			$ (19,997)
Ionis' stand-alone net income			18,785
Net loss available to Ionis common stockholders			$ (1,212)
Weighted average shares outstanding			125,330
Basic net loss per share			$ (0.01)

Three Months Ended June 30 , 2018	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	60,832	$ (0.72)	$ (43,814)
Akcea's net loss attributable to our ownership			$ (43,814)
Ionis' stand-alone net income			5,882
Net loss available to Ionis common stockholders			$ (37,932)
Weighted average shares outstanding			128,712
Basic net loss per share			$ (0.29)

Three Months Ended September 30 , 2018	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	65,538	$ (0.73)	$ (47,789)
Akcea's net loss attributable to our ownership			$ (47,789)
Ionis' stand-alone net income			43,226
Net loss available to Ionis common stockholders			$ (4,563)
Weighted average shares outstanding			137,346
Basic net loss per share			$ (0.03)

Three Months Ended December 31 , 2018	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	67,130	$ (0.79)	$ (53,219)
Akcea's net loss attributable to our ownership			$ (53,219)
Ionis' stand-alone net income			372,913
Net income available to Ionis common stockholders			$ 319,694
Weighted average shares outstanding			137,699
Basic net income per share			$ 2.32

(3) We had net income available to Ionis common stockholders for the following periods. 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 those periods.

Diluted common equivalent shares for each of the periods consisted of the following (in thousands except per share amounts):

Three Months Ended March 31, 2019	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 87,543	138,582	$ 0.63
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	2,252	
Shares issuable upon restricted stock award issuance	—	665	
Shares issuable related to our ESPP	—	38	
Shares issuable related to our 1 percent convertible notes	—	—	
Income available to Ionis common stockholders, plus assumed conversions	$ 87,543	141,537	$ 0.62

Three Months Ended September 30, 2019	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 26,158	140,551	$ 0.19
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,993	
Shares issuable upon restricted stock award issuance	—	844	
Shares issuable related to our ESPP	—	20	
Shares issuable related to our 1 percent convertible notes	—	—	
Income available to Ionis common stockholders, plus assumed conversions	$ 26,158	143,408	$ 0.18

Three Months Ended December 31, 2019	Income (Numerator)	Shares (Denominator)	Per-Share Amount
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	12,046	9,527	
Income available to Ionis common stockholders, plus assumed conversions	$ 196,485	153,303	$ 1.28

Three Months Ended December 31, 2018	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 319,694	137,699	$ 2.32
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,254	
Shares issuable upon restricted stock award issuance	—	636	
Shares issuable related to our ESPP	—	7	
Shares issuable related to our 1 percent convertible notes	10,745	10,260	
Income available to Ionis common stockholders, plus assumed conversions	$ 330,439	149,856	$ 2.21

For the three months ended March 31, 2019 and September 30, 2019, the calculation excluded the 1 percent notes because the effect on diluted earnings per share was anti-dilutive.

Exhibit 4.9

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

As of December 31, 2019, Ionis Pharmaceuticals, Inc. (the "Company") had one class of securities, its Common Stock, registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act").

Description of Common Stock

General

The following description of our Common Stock is a summary and does not purport to be complete. It is subject to and qualified in its entirety by reference to our Amended and Restated Certificate of Incorporation, as amended (the "Certificate of Incorporation"), and our Amended and Restated Bylaws (the "Bylaws"), each of which are incorporated by reference as an exhibit to the Annual Report on Form 10-K of which this Exhibit 4.4 is a part. We encourage you to read our Certificate of Incorporation, Bylaws and the applicable provisions of the General Corporation Law of Delaware (the "DGCL") for additional information.

Authorized Capital Stock

Our authorized capital stock consists of 300,000,000 shares of Common Stock, par value $0.001 per share, and 15,000,000 shares of Preferred Stock, par value $0.001 per share. Our board of directors has the authority, without stockholder approval, except as required by the listing standards of The Nasdaq Stock Market LLC, to issue additional shares of our capital stock. In addition, our board of directors has the authority, without further action by our stockholders, to designate the rights, preferences, privileges and restrictions of our Preferred Stock in one or more series.

Voting Rights

Holders of Common Stock are entitled to one vote per share on all matters to be voted upon by the stockholders, including the election of directors. Our Common Stock does not have cumulative voting rights.

Dividend Rights

Subject to the preferential rights of outstanding shares of Preferred Stock, if any, the holders of Common Stock are entitled to receive dividends out of assets legally available at the times and in the amounts that our board of directors may determine from time to time in its discretion.

Classification of the Board of Directors

Our Certificate of Incorporation provides for classified terms for the members of our board of directors. The board of directors is divided into three classes, and each director serves a three-year term.

Liquidation, Dissolution or Winding Up

Subject to the preferential rights of outstanding shares of Preferred Stock, if any, holders of Common Stock will share equally in all assets legally available for distribution, after payment of all liabilities, to our stockholders in the event of liquidation, dissolution or winding up of the Company.

Other Rights and Preferences

Our Common Stock has no sinking fund or redemption provisions or preemptive, conversion or exchange rights.

Anti-Takeover Provisions

Delaware Anti-takeover Law

We are subject to Section 203 of the DGCL, which prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, unless:

- the transaction is approved by the board of directors before the date the interested stockholder attained that status;
- upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced; or
- on or after the date the business combination is approved by the board and authorized at a meeting of stockholders by at least 66-2/3% of the outstanding voting stock that is not owned by the interested stockholder.

A “business combination” is defined to include any merger or consolidation involving a corporation and the interested stockholder; any sale, transfer, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation; subject to exceptions, any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder; and the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, an “interested stockholder” is an entity or person who, together with affiliates and associates, owns (or within three years prior to the determination of interested stockholder status, did own) 15% or more of a corporation’s voting stock.

The fair price provision and Section 203 of the DGCL could prohibit or delay mergers or other takeover or change in control attempts with respect to us and, accordingly, may discourage attempts to acquire us even though such a transaction may offer our stockholders the opportunity to sell their stock at a price above the prevailing market price.

Certificate of Incorporation and Bylaws Provisions

Our Certificate of Incorporation includes a provision that requires at least 66-2/3% 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.

Provisions of our Certificate of Incorporation and Bylaws may delay or discourage transactions involving an actual or potential change in our control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares or transactions that our stockholders might otherwise deem to be in their best interests. Therefore, these provisions could adversely affect the price of our common stock. Among other things, our Certificate of Incorporation and Bylaws:

- permit our board of directors to issue up to 15,000,000 shares of Preferred Stock, with any rights, preferences and privileges as they may designate;

- provide that the authorized number of directors shall be fixed exclusively by the board of directors;

- provide that the board of directors or any individual director may only be removed with cause by the affirmative vote of the holders of at least a majority of the outstanding common stock or without cause by the affirmative vote of the holders of at least 66-2/3% of the voting power of all of our then outstanding common stock;

- provide that all vacancies, including newly created directorships, may, except as otherwise required by law or subject to the rights of holders of preferred stock as designated from time to time, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum, unless the board of directors determines by resolution that any such vacancies or newly created directorships shall be filled by stockholders;

- classifies our board of directors into three classes;

- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent or electronic transmission;

- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide notice in writing in a timely manner and also specify requirements as to the form and content of a stockholder's notice;

- do not provide for cumulative voting rights (therefore allowing the holders of a majority of the shares of Common Stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose); and

- provide that special meetings of our stockholders may be called only by the chairman of the board, our Chief Executive Officer or by the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors (whether or not there exists any vacancies).

The foregoing provisions may make it more difficult for our existing stockholders to replace our board of directors as well as for another party to obtain control of us by replacing our board of directors. Since our board of directors has the power to retain and discharge our officers, these provisions could also make it more difficult for existing stockholders or another party to effect a change in management. In addition, the authorization of undesignated Preferred Stock makes it possible for our board of directors to issue Preferred Stock with voting or other rights or preferences that could impede the success of any attempt to change our control.

These provisions are intended to enhance the likelihood of continued stability in the composition of our board of directors and its policies and to discourage certain types of transactions that may involve an actual or threatened acquisition of us. These provisions are also designed to reduce our vulnerability to an unsolicited acquisition proposal and to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and may have the effect of deterring hostile takeovers or delaying changes in our control or management. As a consequence, these provisions also may inhibit fluctuations in the market price of our stock that could result from actual or rumored takeover attempts.

Choice of Forum

Our Bylaws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery does not have jurisdiction, another state court located within the State of Delaware or, if no state court located within the State of Delaware has jurisdiction, the federal district court for the District of Delaware) shall, to the fullest extent permitted by law, be the sole and exclusive forum for (i) any derivative action or proceeding brought on behalf of the Company; (ii) any action asserting a claim of breach of a fiduciary duty owed by any director, officer or other employee of the Company to the Company or the Company's stockholders; (iii) any action asserting a claim against the Company or any director or officer or other employee of the Company arising pursuant to any provision of the DGCL, the Certificate of Incorporation (as may be amended from time to time) or the Bylaws (as may be amended from time to time); and (iv) any action asserting a claim against the Company or any director or officer or other employee of the Company governed by the internal affairs doctrine. This choice of forum provision does not apply to suits brought to enforce a duty or liability created by the Securities Act of 1933, as amended, or the Exchange Act, as amended, or any claim for which the federal courts have exclusive jurisdiction. Any person or entity purchasing or otherwise acquiring any interest in shares of capital stock of the Company shall be deemed to have notice of and consented to the provisions of Article XV of the Bylaws.

Exhibit 10.70

CERTAIN IDENTIFIED INFORMATION HAS BEEN EXCLUDED FROM THE EXHIBIT BECAUSE IT IS BOTH (I) NOT MATERIAL AND (II) WOULD BE COMPETITIVELY HARMFUL IF PUBLICLY DISCLOSED. SUCH EXCLUDED INFORMATION HAS BEEN MARKED WITH "[***]".

October 4, 2019

Pfizer Inc.
235 East 42nd Street
New York, NY 10017
Attention: Morris J. Birnbaum, M.D., Ph.D.

Akcea Therapeutics, Inc.
22 Boston Wharf Road
9th Floor
Boston, MA 02210
Attention: Damien McDevitt, Ph.D.

Re: AKCEA-ANGPTL3-L$_{Rx}$ License Agreement

Dear Dr. Birnbaum and Dr. McDevitt:

This letter agreement ("***Letter Agreement***") is in reference to the License Agreement (the "***Agreement***"), dated October 4, 2019, by and between Akcea Therapeutics, Inc. ("***Akcea***") and Pfizer Inc. ("***Pfizer***"), which Agreement includes a sublicense of certain rights licensed by Akcea from its Affiliate, Ionis Pharmaceuticals, Inc. ("***Ionis***"), under the Development, Commercialization and License Agreement, dated December 18, 2015, by and between Ionis (formerly known as Isis Pharmaceuticals, Inc.) and Akcea (the "***Ionis/Akcea License Agreement***"). Any capitalized terms not defined in this Letter Agreement will have the meanings set forth in the Agreement, unless expressly specified otherwise. This Letter Agreement will become effective on the Closing Date of the Agreement.

1. Consent. Pursuant to Section 4.2 of the Ionis/Akcea License Agreement, Ionis hereby consents to Akcea entering into the Agreement.

ionispharma.com

2855 Gazelle Court
Carlsbad, CA 92010

(760) 931-9200

2. Potential Follow-On Compounds. After the Execution Date, subject to Article 6 (Exclusivity) of the Agreement and the terms of this Letter Agreement, Ionis may conduct discovery activities on any compound, other than AKCEA-ANGPTL3-L_{Rx}, that is designed to bind to the RNA that encodes ANGPTL3 (each such compound, a "***Potential Follow-On Compound***"), and may conduct pre-clinical research and pre-clinical development on each such Potential Follow-On Compound. Ionis will provide written notice identifying and disclosing each Potential Follow-On Compound to Pfizer at each Development Update Meeting or sooner if a Potential Follow-On Compound has otherwise been identified.

3. ROFN for Potential Follow-On Compound Collaboration. At any time on or after the Closing Date through the expiration of the Exclusivity Period (the "***ROFN Period***"), Pfizer may, on a one-time basis for each Potential Follow-On Compound, send written notice to Ionis requesting that Ionis and Pfizer enter into a collaboration to conduct research to discover, identify and Exploit a Potential Follow-On Compound (such notice the "***Collaboration Request Notice***"). Upon Ionis' receipt of the Collaboration Request Notice, Pfizer and Ionis will negotiate in good faith commercially reasonable terms for such collaboration for a period of not less than [***] days (the "***Collaboration Negotiation Period***"). If Pfizer and Ionis cannot reach agreement during the Collaboration Negotiation Period, or if Pfizer does not exercise its right to negotiate under this paragraph 3 of this Letter Agreement before the expiration of the ROFN Period, then Ionis will have no further obligation to Pfizer under this paragraph 3 with respect to such Potential Follow-On Compound. For clarity, except as set forth in Section 6.2.1 and Section 6.2.2 of the Agreement, Ionis will not work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to the clinical development or Commercialization of a Potential Follow-On Compound until the Exclusivity Period expires.

4. Attendance at Meetings between Akcea and Pfizer. Ionis has the right, but not the obligation, to attend any meetings between Akcea and Pfizer described in Schedule 4.1 (Project Management Activities) of the Agreement.

5. Pfizer Designee to the Ionis/Akcea Joint Patent Committee. Pfizer hereby designates [***], as Pfizer's initial designee to the JPC (as such term is defined in the Ionis/Akcea License Agreement) solely with respect to the Product, pursuant to the last sentence of Section 9.1.2 of the Ionis/Akcea License Agreement. Pfizer may replace its designee to the JPC (as such term is defined in the Ionis/Akcea License Agreement) at any time by written notice to Ionis and Akcea. For clarity, Pfizer's designee to the JPC will not have any right to attend those portions of JPC meetings that do not concern the Product.

6. Ionis Covenants between Execution and Closing. From the Execution Date and until the Closing Date or the earlier termination of the Agreement in accordance with Article 13 (Term and Termination) of the Agreement, except as consented to in writing by Pfizer, (a) Ionis will conduct its business in the ordinary course of business consistent with past practice and in accordance with all applicable Laws with respect to the performance of its obligations under this Letter Agreement, and (b) Ionis will not (i) [***], and, in addition, will not [***]; (ii) [***]; and (iii) enter into, modify, extend, renew or amend any contract that by its terms expressly limits or impairs in any material manner the ability of Ionis to carry out its obligations under this Letter Agreement or the ability of Akcea to carry out its obligations under the License Agreement.

7. Intellectual Property. Ionis will fulfill the obligations of Akcea as set forth in Article 9 (Intellectual Property) of the Agreement, to the extent that Ionis, rather than Akcea, has the requisite rights to fulfill such obligations under the Ionis/Akcea License Agreement.

8. New Agreements. Ionis will not enter into any new agreement or other obligation with any Third Party, or amend an existing agreement with any Third Party, in each case that restricts, limits or encumbers the rights granted to Pfizer under the Agreement.

9. Formulation or Delivery Technology. If, after the Closing Date, Ionis or its Affiliates becomes the owner or otherwise acquires Control of any formulation or delivery technology that would be necessary or useful in order for Pfizer to further Develop, Commercialize or Exploit the Product, Ionis will make such technology available to Pfizer on commercially reasonable terms.

10. Application of Additional Provisions of the Agreement to Ionis.

(a) To the extent that Ionis is expressly referenced or is referenced in its capacity as an Affiliate of Akcea in the Additional Provisions, Ionis hereby agrees to be bound by and to comply with such provisions as if it was a Party to the Agreement for such purposes. Additionally, to the extent that Ionis is not expressly referenced in the Additional Provisions, Ionis hereby agrees to be bound by and to comply with such Additional Provisions as if it was a Party to the Agreement for such purposes.

(b) "***Additional Provisions***" means the following provisions of the Agreement: Section 2.8.2 (Akcea Regulatory Transfer Cooperation), Section 2.9 (Technology Transfer), Section 2.10 (Class Generic Claims for the Product), Section 2.11.3 (Ionis' Internal Antisense Safety Database), Section 3.2 (Manufacturing Transition Assistance), Section 3.3 (Transfer of Existing Inventory), Section 5.1 (License Grant), Section 5.2 (Pfizer's Sublicensing Rights), Section 5.3 (Requests to Grant Sublicense to CMOs), Article 6 (Exclusivity Provisions), Article 10 (Confidentiality) and Article 11 (Representations and Warranties), *provided*, *however*, that the [***] hours of no-cost manufacturing transition assistance set forth in Section 3.2 (Manufacturing Transition Assistance) of the Agreement and the [***] hours of no-cost regulatory transfer assistance set forth in Section 2.8.2 (Akcea Regulatory Transfer Cooperation) of the Agreement are aggregate caps such that hours contributed by Ionis or Akcea will count toward each such cap, as applicable.

(c) Article 14 (Miscellaneous) and Section 13.4 of the Agreement shall apply to this Letter Agreement *mutatis mutandis*.

11. Indemnification.

(a) Ionis is an intended third party beneficiary with respect to Section 12.1 (Indemnification by Pfizer) of the Agreement.

(b) Ionis hereby agrees to defend, and indemnify and hold harmless, the Pfizer Indemnified Parties from and against any and all Losses, to the extent arising out of or resulting from any Third Party Claims to the extent based upon:

(i) any breach of any representation, warranty or covenant made by Ionis in this Letter Agreement;

(ii) the Exploitation of the Product by Ionis or its Affiliates, subcontractors or Sublicensees, to the extent applicable; or

(iii) the gross negligence or willful misconduct by Ionis in the exercise of its rights or performance of its obligations hereunder;

provided that, in the case of each of paragraph 11(b)(i) through 11(b)(iii) above, Ionis will not be obligated to so defend, and indemnify and hold harmless, the Pfizer Indemnified Parties for any Third Party Claims to the extent that Pfizer has an obligation to indemnify the Akcea Indemnified Parties under Section 12.1 (Indemnification by Pfizer) of the Agreement.

(c) Section 12.3 (Procedure) and Section 12.5 (Damages Waiver) of the Agreement shall apply to this Letter Agreement *mutatis mutandis*.

(d) Notwithstanding anything to the contrary in the Agreement or this Letter Agreement, Pfizer's obligation to indemnify Ionis pursuant to paragraph 11(a) of this Letter Agreement is not duplicative of or in addition to Pfizer's indemnification obligation pursuant to Section 12.1 (Indemnification by Pfizer) of the Agreement. For the avoidance of doubt, neither this Letter Agreement nor the Agreement shall permit a duplicate claim for indemnification or a duplicate payment of Losses arising from the same facts and circumstances giving rise to a pending or previously made claim for indemnification as a claim for indemnification pursuant to either paragraph 11(a) of this Letter Agreement or Section 12.1 (Indemnification by Pfizer) of the Agreement.

12. Incorporation by Reference. Article 1 (Definitions) is hereby incorporated herein by reference with the same force and effect as though fully set forth herein.

13. Term. The term of this Side Letter Agreement will be the Term under the Agreement.

14. Effect of Termination of the Agreement. If the Agreement terminates for any reason, Pfizer will, from the effective date of such termination, automatically become a direct licensee of Ionis with respect to the rights licensed to Pfizer by Akcea on the terms substantially the same as the terms set forth in the Agreement.

[*Signature page to follow****]***

If the terms of this Letter Agreement are acceptable, please so indicate by executing a copy of this Letter Agreement and returning it to Ionis.

Very truly yours,

/s/Brett Monia
Brett Monia
Chief Operating Officer
IONIS PHARMACEUTICALS, INC.

AGREED TO AND CONFIRMED BY AKCEA THERAPEUTICS, INC.:

By:/s/Damien McDevitt
Name: Damien McDevitt
Title: Interim Chief Executive Officer

AGREED TO AND CONFIRMED BY PFIZER INC.:

By:/s/Morris J. Birnbaum
Name: Morris J. Birnbaum
Title: SVP-CSO, Internal Medicine

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Akcea Therapeutics, Inc., a Delaware Corporation

Akcea Therapeutics Canada Inc., a Canadian Corporation

Akcea Therapeutics France SAS, a French Company

Akcea Therapeutics Germany GmbH, a German Corporation

Akcea Therapeutics UK Limited, a United Kingdom Limited Private Company

Akcea Securities Corporation., a Massachusetts Corporation

Akcea Therapeutics Ireland Limited, an Irish Private Company

Akcea Therapeutics Portugal, Unipessoal Lda, a Portuguese Company

Akcea Therapeutics Spain SL, a Spanish Company

Akcea Therapeutics Italia SRL, an Italian Company

Isis USA Limited, a United Kingdom Limited Private Company

Osprey Therapeutics, Inc., a Delaware Corporation

PerIsis I Development Corporation, a Delaware Corporation

Symphony GenIsis, Inc., a Delaware Corporation

Ionis Development (Ireland) Limited, an Irish Private Company

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements on Form S-3 (Nos. 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380, 333-141447, 333-151076, 333-188407 and 333-217422) and in the related Prospectuses, as applicable, and in the Registration Statements on Form S-8 (Nos.333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777, 333-151996, 333-160269, 333-168674, 333-176136, 333-184788, 333-190408, 333-207900, 333-219801 and 333-233143) of Ionis Pharmaceuticals, Inc. of our reports dated February 26, 2020, with respect to the consolidated financial statements of Ionis Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Ionis Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2019.

/s/ ERNST & YOUNG LLP

San Diego, California
March 2, 2020

Exhibit 31.1

CERTIFICATION

I, Brett P. Monia, certify that:

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

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

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

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

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

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Dated: March 2, 2020

/s/ BRETT P. MONIA

Brett P. Monia, Ph.D.
Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

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

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

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

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

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

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Dated: March 2, 2020

/s/ ELIZABETH L. HOUGEN

Elizabeth L. Hougen
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Brett P. Monia, the Chief Executive Officer of Ionis Pharmaceuticals, Inc., (the "Company"), and Elizabeth L. Hougen, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the year ended December 31, 2019, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Annual Report and the results of operations of the Company for the period covered by the Annual Report.

Dated: March 2, 2020

/s/ BRETT P. MONIA
Brett P. Monia, Ph.D.
Chief Executive Officer

/s/ ELIZABETH L. HOUGEN
Elizabeth L. Hougen
Chief Financial Officer

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

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Ionis Pharmaceuticals, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.