UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

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

For the fiscal year ended December 31, 2020

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

For the transition period from _____ to _____

Commission file number 000-19125

Ionis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**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.

Large Accelerated Filer ☒	Accelerated Filer ☐
Non-accelerated Filer ☐	Smaller Reporting Company ☐ Emerging Growth Company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Securities Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management assessment of the effectiveness of its internal controls over financial reporting under Section 4049b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report ☒

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

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

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

DOCUMENTS INCORPORATED BY REFERENCE

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

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

FORWARD-LOOKING STATEMENTS

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

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

Summary of Risk Factors

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

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

TRADEMARKS

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

CORPORATE INFORMATION

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

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

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

Item 1. Business

Overview

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

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

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

Commercial Medicines

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

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

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

Medicines in Phase 3 Studies

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

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

COVID-19

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

Our Marketed Medicines – Transformational Medicines Bringing Value to Patients Today

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Drug Discovery and Development

Introduction to Drug Discovery

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

Our Development Projects

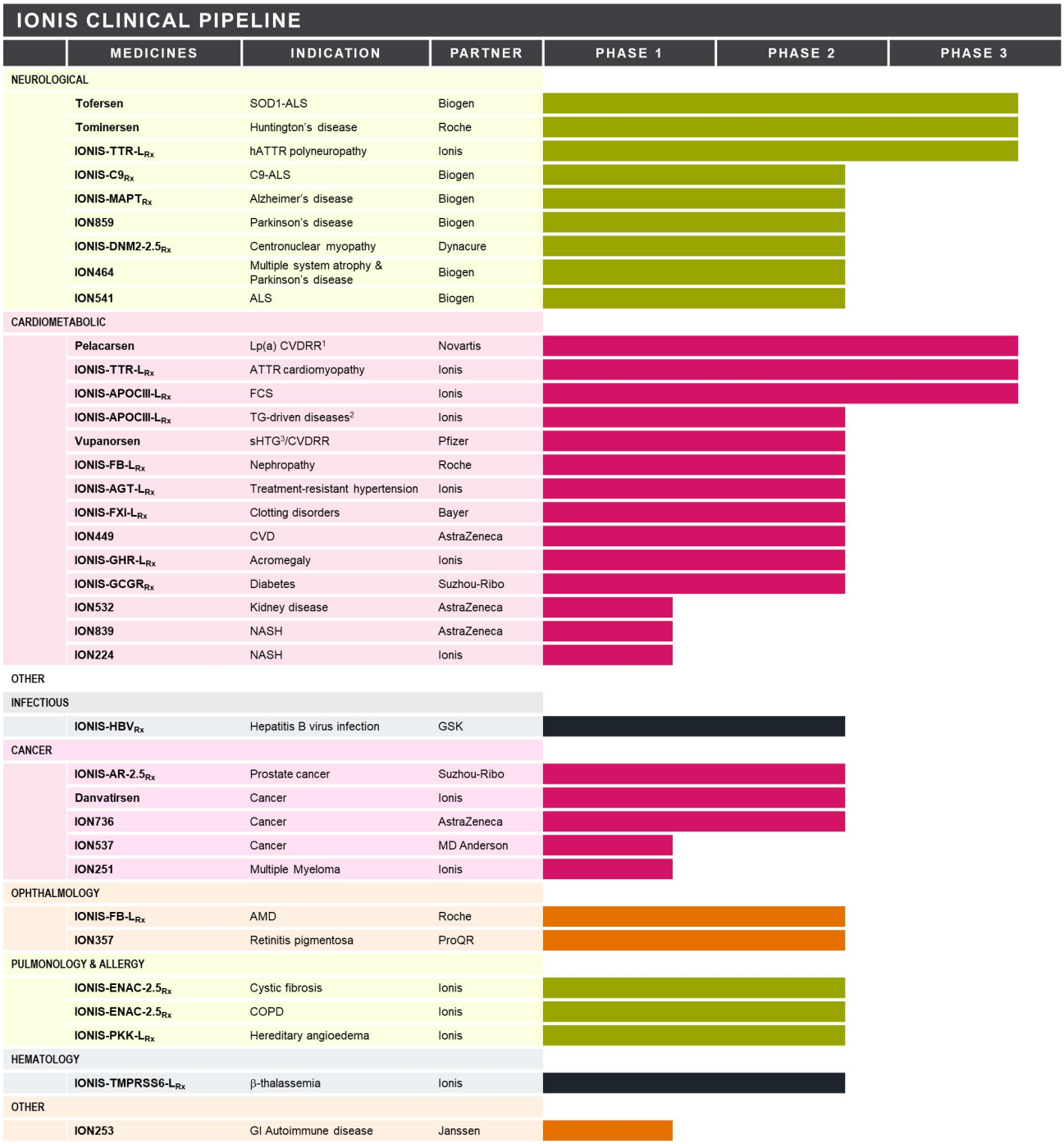
We are a leader in the discovery and development of antisense oligonucleotide medicines, or antisense medicines. By efficiently screening many targets in parallel to select the best candidates and applying our rational approach to selecting disease targets, we have built a robust portfolio of medicines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

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

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

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

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



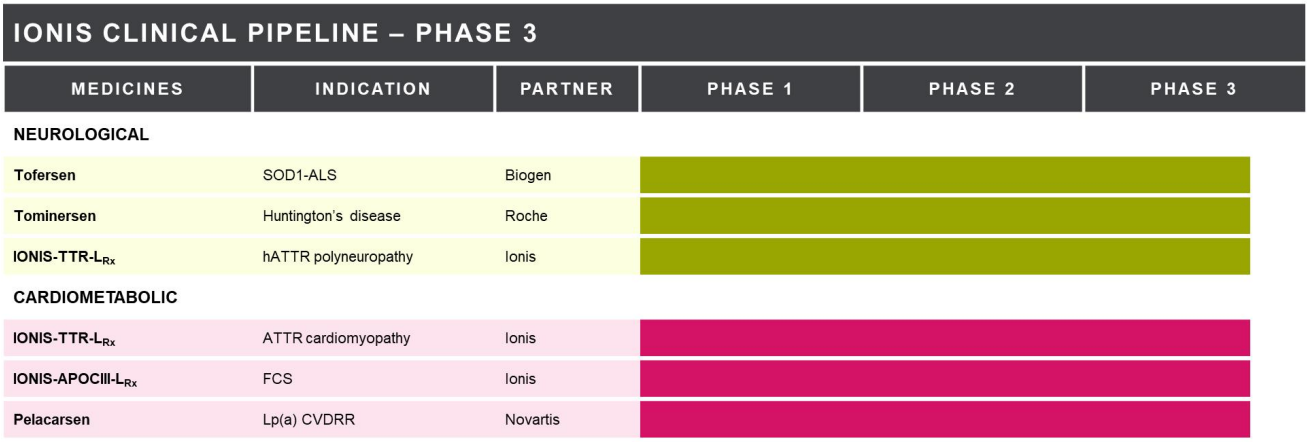
1. CVDRR: Cardiovascular disease risk reduction. 2. TG: Triglyceride. 3. sHTG: Severe hypertriglyceridemia.

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

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

Our Phase 3 Medicines

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



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

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

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

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

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

We completed a randomized, placebo-controlled, dose escalation, Phase 1/2 clinical study of tominersen in patients with early stage HD. In this study, we observed dose-dependent reductions of mHTT among patients treated with tominersen. Tominersen also demonstrated a favorable safety and tolerability profile in this Phase 1/2 clinical study. In March 2018, we reported data from the study that demonstrated substantial reductions in the mHTT as observed in the cerebral spinal fluid, or CSF. The reductions in mHTT were in the target range that produced disease reversal in preclinical models of HD. Tominersen was the first medicine to demonstrate disease-modifying potential by lowering the root cause of HD, the mHTT protein. There were no serious adverse events reported and no participants discontinued from the study. The data from this study were published in *The New England Journal of Medicine* in May 2019.

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

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

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

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

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

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

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

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

IONIS-APOCIII-L_{Rx} – IONIS-APOCIII-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of apoC-III for patients who are at risk of disease due to elevated triglyceride levels. ApoC-III is a protein produced in the liver that regulates triglyceride metabolism in the blood. People with severely elevated triglycerides, such as people with FCS, are at high risk for acute pancreatitis and an increased risk of CVD. ApoC-III is also the target of WAYLIVRA (volanesorsen), the only medicine approved for the treatment of people with FCS. See the WAYLIVRA summary under “Our Marketed Medicines” section for more information about FCS.

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

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

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

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

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

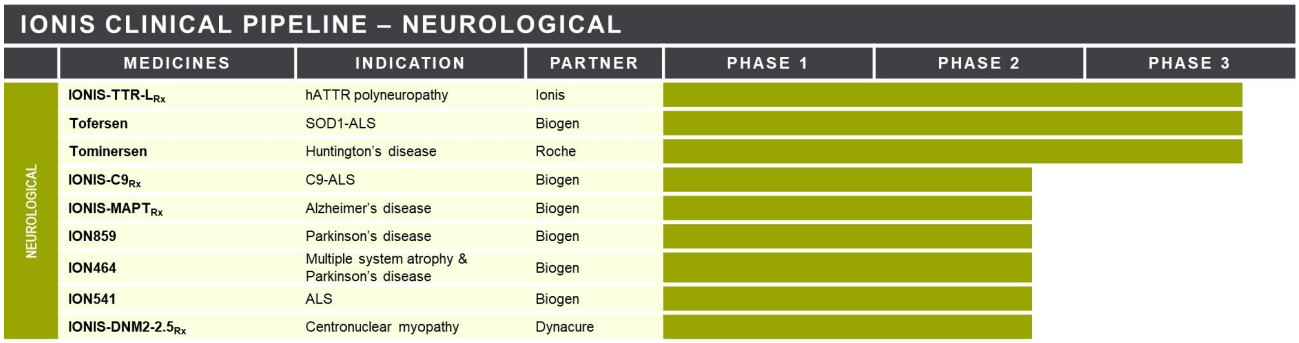
We reported results of the Phase 2 study with pelacarsen in patients with hyperlipoproteinemia(a) at the American Heart Association, or AHA, annual meeting in November 2018. In this clinical study, we observed statistically significant and dose dependent reductions from baseline in Lp(a) levels. Approximately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

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

Neurological Disease Medicines in Development

We are discovering and developing antisense medicines to treat people with neurological diseases. Our neurological medicines address a broad range of diseases in major regions of the brain and all central nervous system, or CNS, cell types. Our antisense medicines aim to address both large and rare patient populations. We are currently investigating potential disease-modifying treatments for common neurological diseases including, Alzheimer's disease and Parkinson's disease. We also have multiple investigational medicines in clinical trials for rare neurological diseases, including ALS and hATTR polyneuropathy. According to the National Institute of Neurological Disorders and Stroke, or NINDS, at the National Institutes of Health, or NIH, a third of the 7,000 known rare diseases are neurological disorders or thought to include a neurological component.

IONIS' Neurological Disease Clinical Pipeline



Wholly Owned Medicines

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

Partnered Medicines

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

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

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

We and Biogen are collaborating to develop IONIS-C9$_{Rx}$ to treat patients with this genetic form of ALS. In August 2018, Biogen initiated a Phase 1/2 clinical study evaluating IONIS-C9$_{Rx}$ in adult patients with C9ORF72-ALS. The current study is a randomized, blinded, placebo-controlled study designed to assess the safety, tolerability, and pharmacokinetics of multiple ascending doses of IONIS-C9$_{Rx}$ administered intrathecally. IONIS-C9$_{Rx}$ is the second medicine from our Biogen collaboration targeting a genetic form of ALS. The first is tofersen, our medicine we designed to treat SOD1 related ALS, caused by a mutation in the *SOD1* gene.

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

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

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

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

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

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

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

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

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

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

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

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

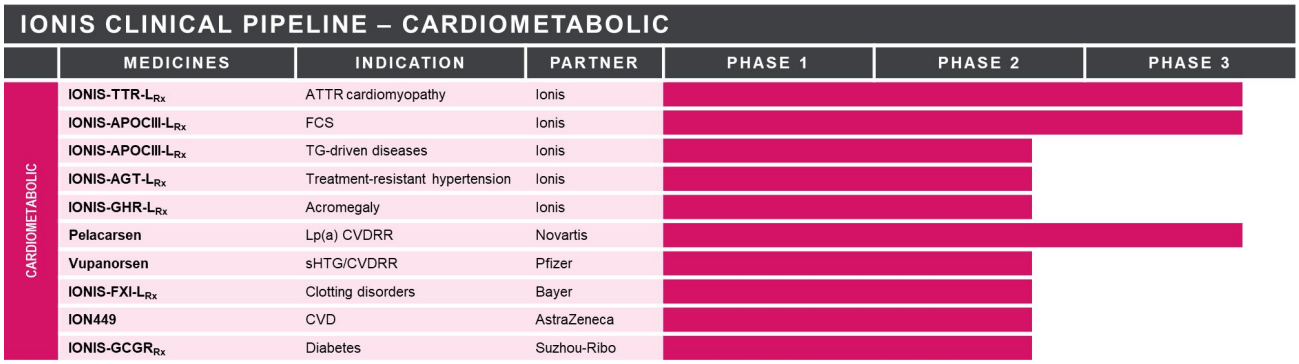
DNM2 reduction demonstrated improved muscle mass and muscle force, and extended lifespan in animal models of the most severe form of CNM.

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

Cardiometabolic Disease Medicines in Development

Developing medicines targeting CVD and metabolic disorders are important areas of focus for us. According to the World Health Organization, or WHO, CVD remains the number one cause of death globally. An estimated 17.9 million people died from CVD in 2016, representing approximately 30 percent of all deaths globally. Our cardiovascular medicines target the major risk factors of cardiovascular disease, including cholesterol, triglycerides and hypertension. Metabolic disorders, such as nonalcoholic steatohepatitis, or NASH, are chronic diseases that affect tens of millions of people. There is a significant need for new therapies for these people. According to the American Liver Foundation, nonalcoholic fatty liver disease, or NAFLD, is the most common chronic liver condition in the U.S. It is estimated that about 25 percent of adults in the U.S. have NAFLD. Of those with NAFLD, about 20 percent have NASH or about 5% of adults in the U.S.

IONIS' Cardiometabolic Disease Clinical Pipeline



Wholly Owned Medicines

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

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

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

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

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

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

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

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

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

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

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

Partnered Medicines

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

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

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

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

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

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

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

IONIS-FXI-L_{Rx} – IONIS-FXI-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of Factor XI. Factor XI is a clotting factor produced in the liver that is important in the growth of blood clots. High levels of Factor XI increase the risk of thrombosis. Thrombosis, characterized by the formation of a blood clot inside blood vessels, can cause heart attacks and strokes. People who are deficient in Factor XI have a lower incidence of thromboembolic events with minimal increase in bleeding risk. Although currently available anticoagulants reduce the risk of thrombosis, physicians associate these anticoagulants with increased bleeding, which can be fatal. By inhibiting Factor XI production, we believe that IONIS-FXI-L_{Rx} can be used broadly as an anti-thrombotic in many different therapeutic settings for which additional safe and well tolerated anti-thrombotic medicines are needed.

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

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

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

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

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

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

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

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

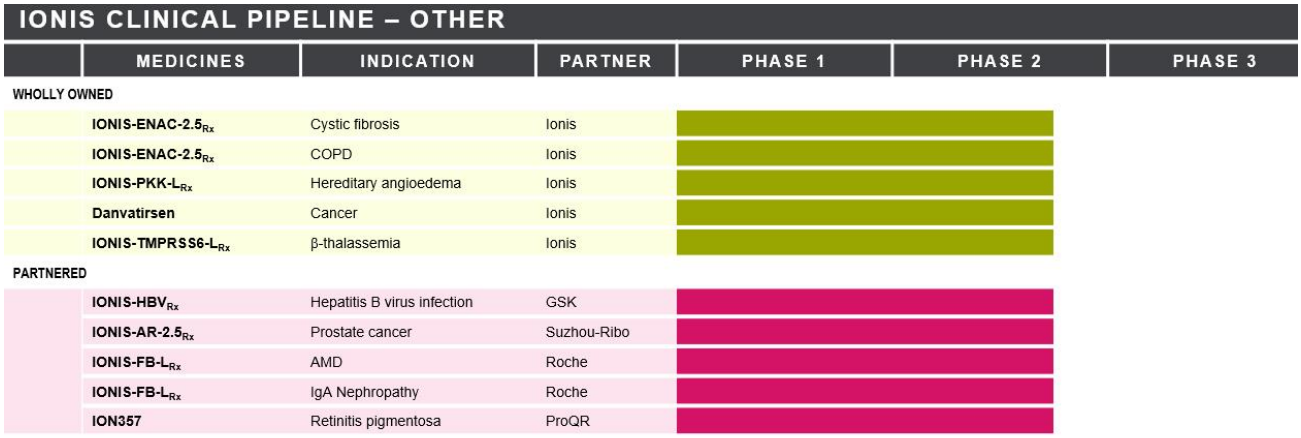
Diabetes is a chronic disease in which the blood glucose levels are too high. Although glucose is an important source of energy for your body and is vital to your health, uncontrolled increases in glucose can lead to serious health problems, such as diabetes. Diabetes is separated into type 1 and type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

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

Other Medicines in Development

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

IONIS' Other Medicines in Clinical Pipeline



Wholly Owned Medicines

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

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

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

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

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

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

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

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

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

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

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

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

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

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

β-thalassemia can be further subdivided into patients with transfusion-dependent thalassemia, or TDT, and non-transfusion dependent thalassemia, or 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 a randomized, blinded, placebo-controlled, dose-escalation Phase 1 study in healthy volunteers, we demonstrated dose-dependent reductions of serum iron and serum transferrin saturation. Additionally, we observed an increase in serum hepcidin and predicted changes in hemoglobin. IONIS-TMPRSS6-L_{Rx} demonstrated a favorable safety and tolerability profile. In December 2018, we presented positive Phase 1 data at the American Society of Hematology Annual Meeting.

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

Partnered Medicines

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

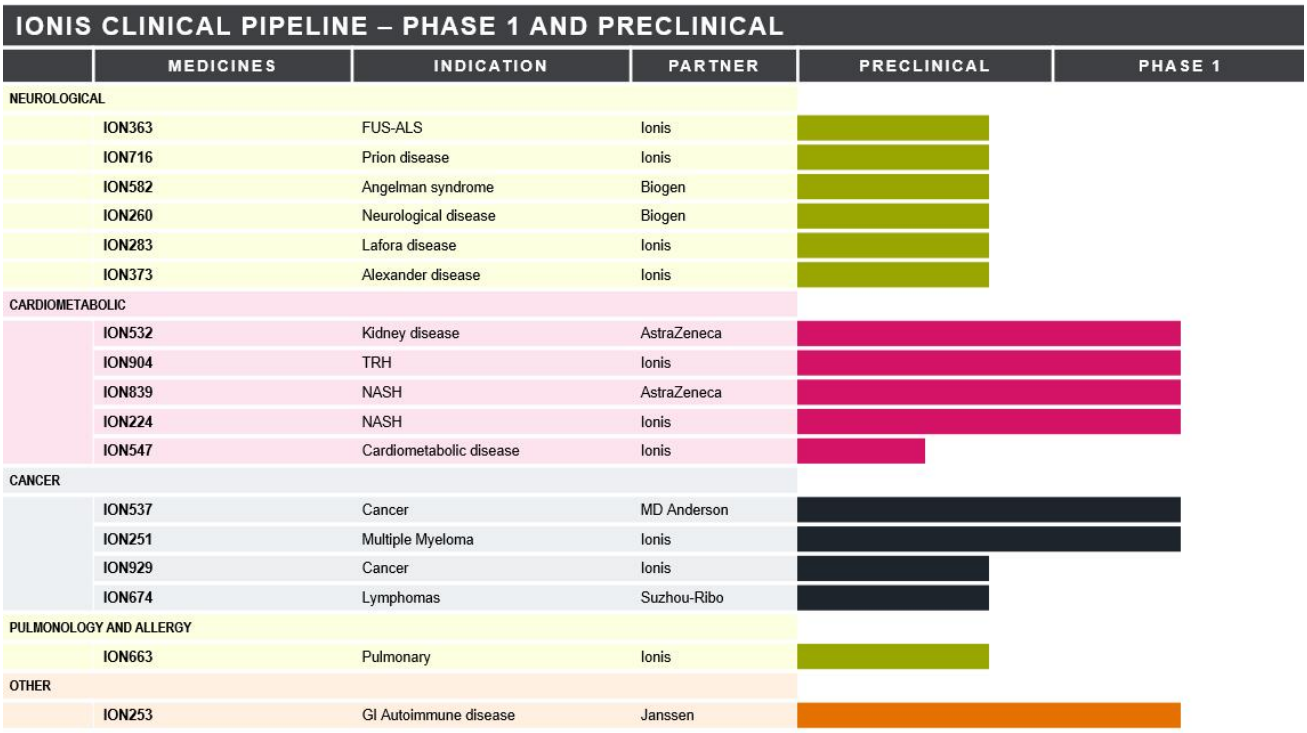
Retinitis pigmentosa, or RP, is a group of rare inherited eye disorders causing photoreceptor degeneration that leads to progressive vision loss. Photoreceptors are cells in the eye's retina responsible for converting light into signals that are sent to the brain. Photoreceptors provide us our color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

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

Phase 1 Medicines in Clinical Development

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

IONIS' Phase 1 and Preclinical Pipeline



Antisense Technology

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

These advantages include:

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

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

Technology Overview

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

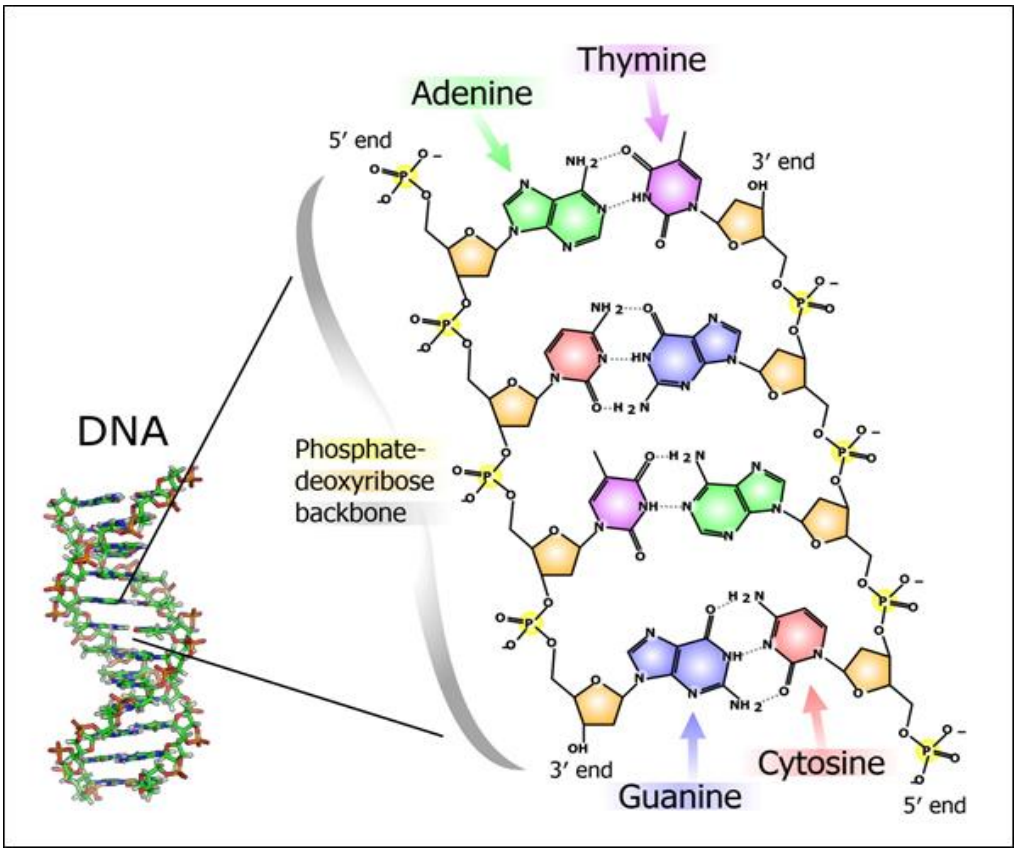


Figure 1: Illustration of DNA.

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

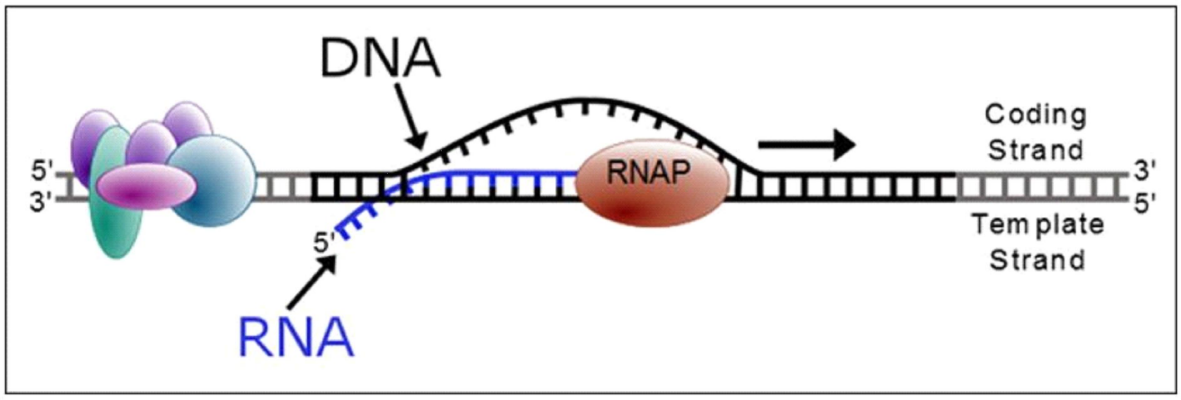


Figure 2: Transcription of information contained in a gene, or DNA, to RNA.

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

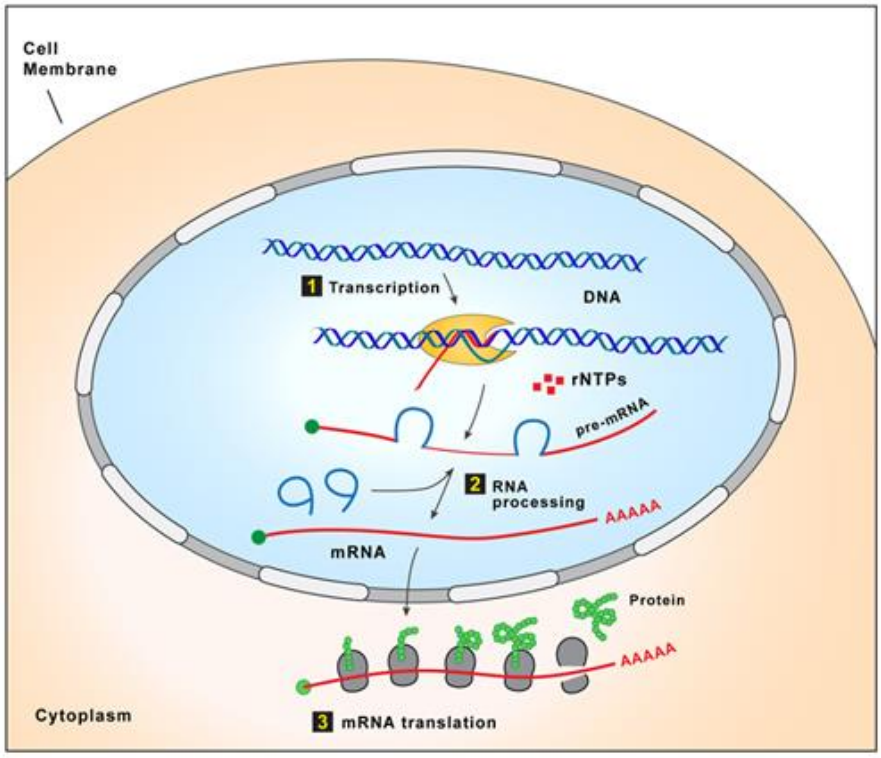


Figure 3: Translation of the protein-coding information contained in mRNA to protein.

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

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

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

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

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

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

Antisense Targets and Mechanisms

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

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

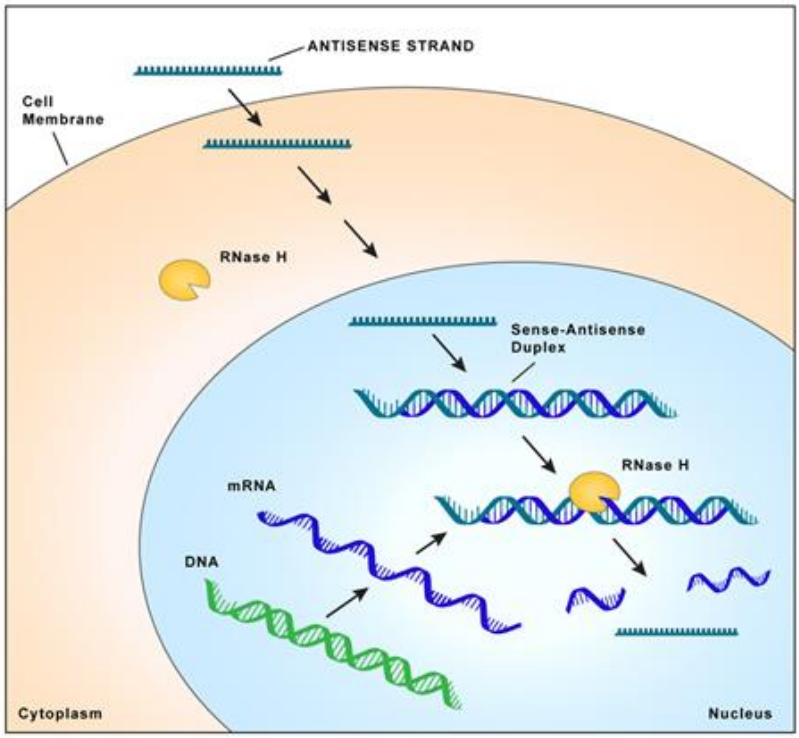


Figure 4: Antisense medicine using the RNase H mechanism of action.

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

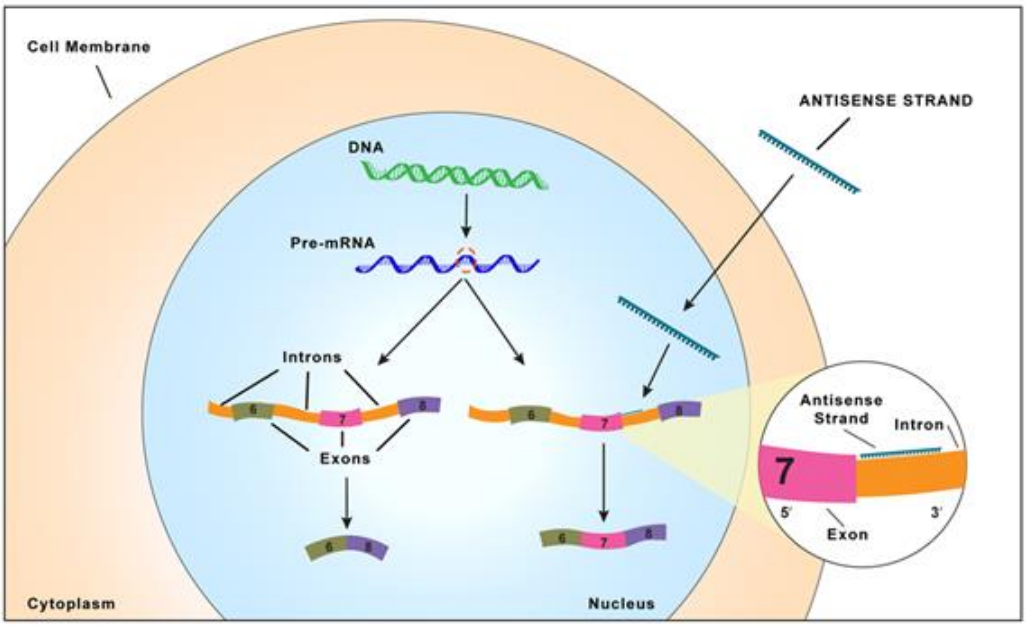


Figure 5: Antisense medicine altering splicing of the SMN2 mRNA.

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

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

Collaborative Arrangements

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

Strategic Partnership

Biogen

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

Spinal Muscular Atrophy Collaborations

SPINRAZA

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

New antisense medicines for the treatment of SMA

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

Neurology Collaborations

2018 Strategic Neurology

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

2013 Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license medicines resulting from this collaboration. We will usually be responsible for drug discovery and early development of antisense medicines and Biogen will have the option to license antisense medicines after Phase 2 proof-of-concept. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. We are currently advancing six investigational medicines in development under this collaboration, including a medicine for Parkinson's disease, three medicines for ALS, a medicine for multiple system atrophy and a medicine for an undisclosed target. In December 2018, Biogen exercised its option to license our most advanced ALS medicine, tofersen, and as a result Biogen is now responsible for global development, regulatory and commercialization activities and costs for tofersen.

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

2012 Neurology

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

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

Research, Development and Commercialization Partners

AstraZeneca

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

Cardiovascular, Renal and Metabolic Diseases Collaboration

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

- ION449 (formerly IONIS-AZ4-2.5-L_{Rx}), an investigational medicine we designed to reduce the liver production of PCSK9 and lower the plasma level of LDL-C and thus reduce the risk of cardiovascular disease;
- ION532, an investigational medicine we designed to reduce the production of APOL1 for the treatment of APOL1-associated chronic kidney disease;
- ION839, an investigational medicine we designed to inhibit the production of PNPLA3 protein, a major genetic determinant of NASH progression; and
- ION455, an investigational medicine we designed as a potential treatment for NASH.

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

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

Oncology Collaboration

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

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

Bayer

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

GSK

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

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

Janssen Biotech, Inc.

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

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

Novartis

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

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

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

Pfizer

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

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

PTC Therapeutics

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

Roche

Huntington's Disease

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

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

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

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

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

Other Agreements

Alnylam Pharmaceuticals, Inc.

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

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

The Ludwig Institute; Center for Neurological Studies

We have a collaboration with the Ludwig Institute, the Center for Neurological Studies and researchers to discover and develop antisense medicines for ALS and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and the Center for Neurological Studies modest milestone payments and royalties on any antisense medicines resulting from the collaboration.

Manufacturing

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

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

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

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

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

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

SPINRAZA

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

TEGSEDI and WAYLIVRA

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

Tominersen

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

Tofersen

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

Pelacarsen

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

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

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

LICA Medicines

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

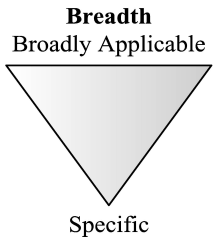
Patents and Proprietary Rights

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

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

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	Certain MOE nucleosides and oligonucleotides containing these nucleotides
United States	7,399,845	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
United States	7,741,457	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
United States	8,022,193	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Oligonucleotides containing cEt nucleoside analogs
Europe	1984381	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
Europe	2314594	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Oligonucleotides containing cEt nucleoside analogs and methods of use
Japan	5342881	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
United States	7,569,686	COMPOUNDS AND METHODS FOR SYNTHESIS OF BICYCLIC NUCLEIC ACID ANALOGS	2027	Methods of synthesizing cEt nucleosides

Antisense Drug Design Motifs

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

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

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

LIgand-Conjugated Antisense (LICA) Technology

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

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 products specifically, in addition to the broader core antisense patents described above.

SPINRAZA and Survival Motor Neuron

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

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

TEGSEDI and Transthyretin

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

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 issued patents claiming the specific sequence and chemical composition of WAYLIVRA in the U.S. and Europe. We believe the issued claims protect WAYLIVRA from generic competition in the U.S. and Europe until at least 2023 and 2024, respectively. We are pursuing additional patent applications designed to protect WAYLIVRA worldwide. The table below lists some key issued patents protecting WAYLIVRA in the U.S. and Europe:

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 C-III (APOCIII) EXPRESSION	2032	Methods of using ApoCIII antisense oligonucleotides for reducing pancreatitis and chylomicronemia and increasing HDL
United States	9,593,333	MODULATION OF APOLIPOPROTEIN C-III (APOCIII) EXPRESSION IN LIPOPROTEIN LIPASE DEFICIENT (LPLD) POPULATIONS	2034	Methods of treating lipoprotein lipase deficiency with an ApoCIII specific inhibitor wherein triglyceride levels are reduced
Europe	2956176	MODULATION OF APOLIPOPROTEIN C-III (APOCIII) EXPRESSION IN LIPOPROTEIN LIPASE DEFICIENT (LPLD) POPULATIONS	2034	ApoCIII specific inhibitors including WAYLIVRA for treating lipoprotein lipase deficiency or familial chylomicronemia syndrome

Tominersen and Huntingtin

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

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

Tofersen and SOD-1

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

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

Pelacarsen and Apo(a)

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

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

IONIS-TTR-L_{Rx} and Transthyretin

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

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

IONIS-APOCIII-L_{Rx}

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

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

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

Manufacturing Patents

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

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

Government Regulation

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

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

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

The FDA must approve any new medicine before a manufacturer can market it in the U.S. In order to obtain approval, we and our partners must complete clinical studies and prepare and submit an NDA to the FDA. If the FDA approves a medicine, it will issue an approval letter authorizing commercial marketing of the medicine and may require a risk evaluation and mitigation strategy, or REMS, to help ensure the benefits of the medicine outweigh the potential risks. For example, TEGSEDI has a REMS program. The requirements for REMS can materially affect the potential market and profitability of our medicines. In foreign jurisdictions, the drug approval process is similarly demanding.

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

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

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

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

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

Sales and Marketing

Numerous regulatory authorities in addition to the FDA, including, in the U.S., the Centers for Medicare and Medicaid Services, other divisions of the U.S. Department of Health and Human Services, the U.S. Department of Justice, and similar foreign, state and local government authorities, regulate sales, promotion and other activities following drug approval. As described above, the FDA regulates all advertising and promotion activities for drugs under its jurisdiction both prior to and after approval. Only those claims relating to safety and efficacy that the FDA has approved may be used in labeling. Physicians may prescribe legally available drugs for uses that are not described in the drug's labeling and that differ from those we tested and the FDA approved. Such off-label uses are common across medical specialties and often reflect a physician's belief that the off-label use is the best treatment for the patients. The FDA does not regulate the behavior of physicians in their choice of treatments, but FDA regulations do impose stringent restrictions on manufacturers' communications regarding off-label uses. If we do not comply with applicable FDA requirements, we may face adverse publicity, enforcement action by the FDA, corrective advertising, consent decrees and the full range of civil and criminal penalties available to the FDA. Promotion of off-label uses of drugs can also implicate the false claims laws described below.

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

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

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

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

Competition

Our Business in General

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

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

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

SPINRAZA

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

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

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

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

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

TEGSEDI and IONIS-TTR-L_{Rx}

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

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

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

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

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

WAYLIVRA and IONIS-APOCIII-L_{Rx}

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

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

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

Tominersen

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

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

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

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

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

Tofersen

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

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

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

Employees & Human Capital

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

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

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

Benefits

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

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

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

Pay Equity

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

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

Diversity, Equity and Inclusion

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

Training and Development

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

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

COVID-19 Response

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

Information about our Executive Officers

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

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

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

Executive Chairman of Ionis' Board of Directors

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

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

BRETT P. MONIA, Ph.D.

Chief Executive Officer

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

C. FRANK BENNETT, Ph.D.

Executive Vice President, Chief Scientific Officer

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

ONAIZA CADORET-MANIER

Executive Vice President, Chief Corporate Development and Commercial Officer

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

RICHARD S. GEARY, Ph.D.

Executive Vice President, Chief Development Officer

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

ELIZABETH L. HOUGEN

Executive Vice President, Finance and Chief Financial Officer

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

PATRICK R. O'NEIL, Esq.

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

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

EUGENE SCHNEIDER, M.D.

Executive Vice President, Chief Clinical Development Officer

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

ERIC E. SWAYZE, Ph.D.

Executive Vice President, Research

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

Item 1A. RISK FACTORS

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

Risks Related to the COVID-19 Pandemic

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

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

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

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

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

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

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

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

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

Risks Related to the Commercialization of our Medicines

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Our medicines could be subject to regulatory limitations following approval.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Our operations are subject to additional healthcare laws.

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

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

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

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

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

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

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

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

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

Risks Related to the Development and Regulatory Approval of our Medicines

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

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

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

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

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

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

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

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

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

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

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

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

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

In addition, our current medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could have, or be perceived by a regulatory authority to have, an impact on a different medicine we are developing. This could cause the FDA and other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our medicines or increase our costs. For example, the FDA or other regulatory agencies could request, among other things, any of the following regarding one of our medicines: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. This happened in connection with the conditional marketing approval for WAYLIVRA in the EU, as the EC is requiring us to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. We have an ongoing OLE extension study of WAYLIVRA in patients with FCS and an OLE study of TEGSEDI in patients with hATTR, and an early access program, or EAP, for WAYLIVRA. Adverse events or results from these studies or the EAPs could negatively impact our pending or future marketing approval applications for WAYLIVRA and TEGSEDI in patients with FCS or hATTR amyloidosis or the commercial opportunity for WAYLIVRA or TEGSEDI.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks Associated with our Businesses as a Whole

Risks related to our financial results

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

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

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

Many of our medicines are undergoing clinical studies or are in the early stages of research and development. Most of our drug programs will require significant additional research, development, manufacturing, preclinical and clinical testing, marketing authorization, preclinical activities and commitment of significant additional resources prior to their successful commercialization. These activities will require significant cash. As of December 31, 2020, we had cash, cash equivalents and short-term investments equal to $1.9 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or to license certain medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

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

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

Risks related to our intellectual property

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

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

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

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

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

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

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

Risks related to our business strategy and personnel

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

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

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

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

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

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

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers that would prevent them from leaving us. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies may make it more challenging to recruit and retain qualified scientific personnel. Similarly, if we cannot recruit and retain qualified marketing, sales and distribution personnel, our ability to effectively implement our new commercial strategy following the Akcea Acquisition will be adversely affected.

Risks related to taxes

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

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

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

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

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

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

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

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

We could be subject to additional tax liabilities.

We are subject to U.S. federal, state, local and sales taxes in the U.S. and foreign income taxes, withholding taxes and transaction taxes in foreign jurisdictions. Significant judgment is required in evaluating our tax positions and our worldwide provision for taxes. During the ordinary course of business, there are many activities and transactions for which the ultimate tax determination is uncertain. In addition, our tax obligations and effective tax rates could be adversely affected by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations, including those relating to income tax nexus, by recognizing tax losses or lower than anticipated earnings in jurisdictions where we have lower statutory rates and higher than anticipated earnings in jurisdictions where we have higher statutory rates, by changes in foreign currency exchange rates, or by changes in the valuation of our deferred tax assets and liabilities. We may be audited in various jurisdictions, and such jurisdictions may assess additional taxes, sales taxes and value-added taxes against us. Although we believe our tax estimates are reasonable, the final determination of any tax audits or litigation could be materially different from our historical tax provisions and accruals, which could have a material adverse effect on our operating results or cash flows in the period for which a determination is made.

General risk factors

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

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

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

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

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

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

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

In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange $375.6 million of our 1% Notes for $439.3 million of our 0.125% Notes, and to issue $109.5 million of our 0.125% Notes. Additionally, in connection with the pricing of our 0.125% Notes, we entered into call spread transactions in which we purchased note hedges and sold warrants. Terminating or unwinding the call spread transactions could require us to make substantial payments to the counterparties under those agreements or may increase our stock price. The costs or any increase in stock price that may arise from terminating or unwinding such agreements could make an acquisition of our company significantly more expensive to the purchaser.

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

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

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

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

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

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

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

We are dependent upon our own and third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity, with third-party phishing and social engineering attacks in particular increasing in connection with the COVID-19 Pandemic. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and state breach notification laws and foreign law equivalents, subject us to financial penalties and mandatory and costly corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, our efforts may not prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

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

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

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

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

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

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

Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we continue to incur additional expenses and divert our management's time to comply with these regulations. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the SEC, the Public Company Accounting Oversight Board, or PCAOB, or The Nasdaq Global Select Market. Any such action could adversely affect our financial results and the market price of our common stock.

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

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

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

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

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

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

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

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

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

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

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

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

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

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

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

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

Item 3. Legal Proceedings

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

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

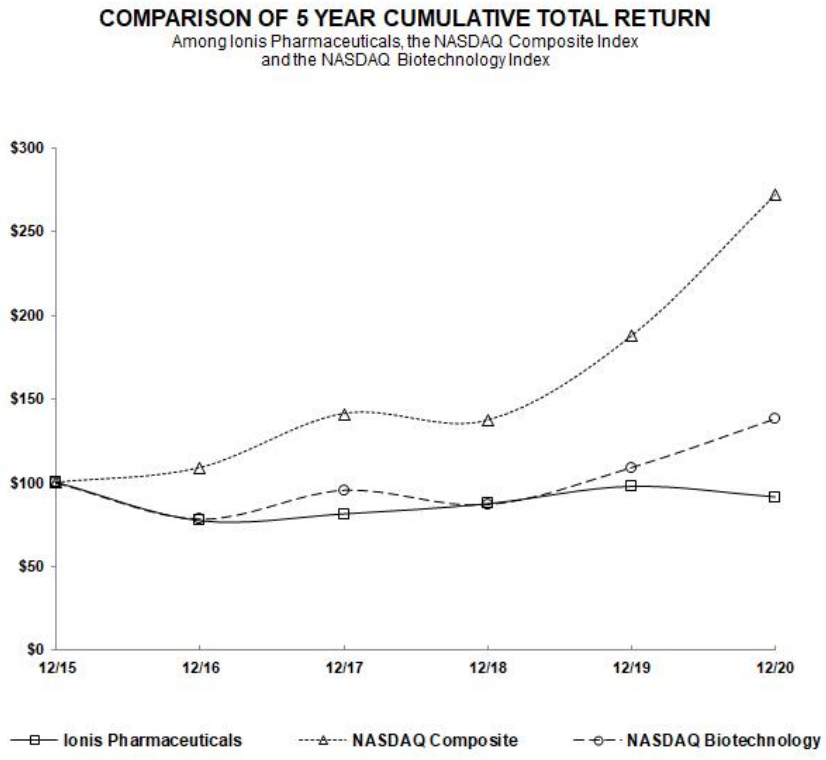
Market Information and Dividends

Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol "IONS." As of February 18, 2021, there were approximately 506 stockholders of record of our common stock. Because many of our shares are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of stockholders represented by these record holders.

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

Performance Graph (1)

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



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

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN
Among Ionis Pharmaceuticals, Inc., the Nasdaq Composite Index,
and the Nasdaq Biotechnology Index

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

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

Item 6. Selected Financial Data

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

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

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

Overview

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

Financial Highlights

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

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

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

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

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

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

Business Segments

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

Critical Accounting Estimates

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

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

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

The following are descriptions of our critical accounting estimates.

Revenue Recognition

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

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

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

Commercial Revenue: Product sales, net

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

Research and development revenue under collaborative agreements

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

- Identifying the performance obligations contained in the agreement

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

- Determining the transaction price, including any variable consideration

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

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

- Allocating the transaction price to each of our performance obligations

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

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

Amortization from Upfront Payments

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

Milestone Payments

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

- Whether the milestone payment is probable (discussed in detail above under "Determining the transaction price, including any variable consideration"); and
- Whether the milestone payment relates to services we are performing or if our partner is performing the services:
- If we are performing services, we recognize revenue over our estimated period of performance in a similar manner to the amortization of upfront payments (discussed above under "Amortization of Upfront payments").
- Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event and we do not have a performance obligation.

License Fees

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

Estimated Liability for Clinical Development Costs

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

Income Taxes

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

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

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

Results of Operations

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

Years Ended December 31, 2020 and December 31, 2019

Revenue

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

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

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

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

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

Operating Expenses

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

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

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

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

Cost of Products Sold

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

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

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

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

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

Research, Development and Patent Expenses

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

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

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

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

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

Antisense Drug Discovery

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

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

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

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

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

Antisense Drug Development

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

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

Our development expenses increased in 2020 compared to 2019 primarily due to our broad Phase 3 program for IONIS-TTR-L_{Rx}, which we initiated in late 2019 and other medicines in our wholly-owned pipeline. These increases were slightly offset by decreases in expenses for TEGSEDI, WAYLIVRA, IONIS-FXI-L_{Rx}, IONIS-APOCIII-L_{Rx} and vupanorsen. We completed a Phase 2 study for IONIS-FXI-L_{Rx} in 2019 and we completed Phase 2 studies for IONIS-APOCIII-L_{Rx} and vupanorsen in early 2020. All amounts exclude non-cash compensation expense related to equity awards.

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

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

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

Manufacturing and Development Chemistry

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

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

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

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

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

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

R&D Support

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

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

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

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

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

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

Selling, General and Administrative Expenses

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

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

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

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

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

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

Akcea Therapeutics, Inc.

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

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

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

Investment Income

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

Interest Expense

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

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

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

Gain on Investments

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

Early Retirement of Debt

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

Income Tax Expense (Benefit)

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

Net Income (Loss)

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

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

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

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

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

Liquidity and Capital Resources

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

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

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

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

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

0.125 Percent Convertible Senior Notes and Call Spread

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

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

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

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

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

	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. In December 2016, we issued an additional $185.5 million of 1% Notes in exchange for the redemption of a portion of our previously outstanding 2¾% Notes. In December 2019, we exchanged a portion of our 1% Notes for new 0.125% Notes.

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

	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.

Research and Development and Manufacturing Facilities

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

Other Obligations

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

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

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

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

Item 8. Financial Statements and Supplementary Data

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

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

None.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

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

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

Management's Report on Internal Control over Financial Reporting

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

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

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

Changes in Internal Control over Financial Reporting

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

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

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

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

Basis for Opinion
The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

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

Definition and Limitations of Internal Control Over Financial Reporting
A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

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

/s/ Ernst & Young LLP

San Diego, California
February 24, 2021

Item 9B. Other Information

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

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

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

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

Delinquent Section 16(a) Reports

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

Item 11. Executive Compensation

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

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

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

Securities Authorized for Issuance under Equity Compensation Plans

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

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)	12,394,777	$ 54.11	8,325,343(b)
Total	12,394,777	$ 54.11	8,325,343

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

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

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
2.1	Agreement and Plan of Merger, dated as of August 30, 2020, among Akcea Therapeutics, Inc., Ionis Pharmaceuticals, Inc. and Avalanche Merger Sub, Inc., filed as an exhibit to the Registrant's Current Report on Form 8-K filed August 31, 2020 and incorporated herein by reference.
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
3.2	Certificate of Amendment to Restated Certificate of Incorporation, filed June 17, 2014. - Filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement, for the 2014 Annual Meeting of Stockholders, filed with the SEC on April 25, 2014 and incorporated herein by reference.
3.3	Certificate of Amendment to Restated Certificate of Incorporation, filed December 18, 2015. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 18, 2015 and incorporated herein by reference.
3.4	Amended and Restated Bylaws, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 18, 2015 and incorporated herein by reference.
4.1	Certificate of Designation of the Series C Junior Participating Preferred Stock, filed as an exhibit to Registrant's Report on Form 8-K filed December 13, 2000 and incorporated herein by reference.
4.2	Specimen Common Stock Certificate, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
4.3	Indenture, dated as of November 17, 2014, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 1.00 percent Convertible Senior Note due 2021, filed as an exhibit to the Registrant's Current Report on Form 8-K filed November 21, 2014 and incorporated herein by reference.
4.4	Indenture, dated as of December 19, 2019, by and between Ionis Pharmaceuticals, Inc. and U.S. Bank National Association, as trustee, including Form of 0.125 percent Convertible Senior Note due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 23, 2019 and incorporated herein by reference.
4.5	Form of Exchange and/or Subscription Agreement for Ionis Pharmaceuticals, Inc. Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.6	Form of Convertible Note Hedge Transactions Confirmation, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.7	Form of Warrant Transactions Confirmation, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.8	Description of the Registrant's Securities, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2019 and incorporated herein by reference.
10.1	Form of Indemnity Agreement entered into between the Registrant and its Directors and Officers with related schedule, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference.
10.2*	Registrant's 1989 Stock Option Plan, as amended, filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2012 Annual Meeting of Stockholders, filed with the SEC on April 16, 2012 and incorporated herein by reference.
10.3*	Registrant's Amended and Restated 2000 Employee Stock Purchase Plan, filed as an exhibit to Registrant's Current Report on Form 8-K filed with the SEC on March 26, 2019 and incorporated herein by reference.

10.4	Form of Employee Confidential Information and Inventions Agreement, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
10.5	Amendment #1 to the Research, Development and License Agreement dated May 11, 2011 by and between the Registrant and Glaxo Group Limited, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2011 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.6	Amended and Restated Collaboration and License Agreement between the Registrant and Antisense Therapeutics Ltd dated February 8, 2008, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2008 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.7	Strategic Collaboration, Option and License Agreement by and among Akcea Therapeutics, Inc. and Novartis Pharma AG, dated January 5, 2017, filed as an exhibit to Akcea Therapeutics, Inc.'s Form S-1 filed March 27, 2017 and incorporated herein by reference.
10.8	Amendment No. 1 to the Strategic Collaboration, Option and License Agreement between Akcea Therapeutics, Inc. and Novartis Pharma AG dated February 22, 2019, filed as an exhibit to Akcea Therapeutics, Inc.'s Quarterly Report on Form 10-Q for the quarter ended March 30, 2019 and incorporated herein by reference.
10.9	Stock Purchase Agreement among the Registrant, Akcea Therapeutics, Inc. and Novartis Pharma AG dated January 5, 2017, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 and incorporated herein by reference.
10.10	Amendment #1 between the Registrant and Bayer AG dated February 10, 2017, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.11	Registrant's Amended and Restated 10b5-1 Trading Plan dated September 12, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013 and incorporated herein by reference.
10.12*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended, filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement for the 2020 Annual Meeting of Stockholders, filed with the SEC on April 24, 2020 and incorporated herein by reference.
10.13*	Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, filed as an exhibit to the Registrant's Form S-8 filed on August 7, 2020 and incorporated herein by reference.
10.14	Research Collaboration, Option and License Agreement between the Registrant and Biogen MA Inc. dated December 19, 2017, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.15*	Amended and Restated Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Notice of 2019 Annual Meeting of Stockholders and Proxy Statement filed with the SEC on April 26, 2019 and incorporated herein by reference.
10.16*	Form of Option Agreement under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference.
10.17*	Form of Time-Vested Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed with the SEC on August 8, 2011 and incorporated herein by reference.
10.18*	Forms of Performance Based Restricted Stock Unit Grant Notice and Performance Based Restricted Stock Unit Agreement for Performance Based Restricted Stock Units granted under the 2011 Equity Incentive Plan.

10.19*	Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.20*	Form of Global Option Agreement for options granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.21*	Form of Global Restricted Stock Unit Agreement for restricted stock units granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.22*	Forms of Restricted Stock Unit Grant Notice, Stock Option Grant Notice and Stock Option Exercise Notice for options granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.23	Loan Agreement between Ionis Gazelle, LLC and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.24*	Form of Option Agreement under the 1989 Stock Option Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference.
10.25*	Form of Option Agreement for Options granted under the 2002 Non-Employee Director's Stock Option Plan, filed as an exhibit to the Registrant's Form S-8 filed on August 7, 2020 and incorporated herein by reference.
10.26	Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated March 30, 2010, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2010 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.27	Loan Agreement between Ionis Faraday, LLC and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.28	Research Agreement dated August 10, 2011 between the Registrant and CHDI Foundation, Inc, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2011 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.29	Guaranty between the Registrant and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.30	Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated January 3, 2012, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.31	DMPK Research, Development, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated June 27, 2012, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.32	Amendment #2 to Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated October 30, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.33	Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated December 7, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.34	Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated December 10, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.35	HTT Research, Development, Option and License Agreement among the Registrant, F. Hoffmann-La Roche Ltd and Hoffman-La Roche Inc. dated April 8, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.36	Letter Agreement between the Registrant and CHDI Foundation, Inc. dated April 8, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.37	Amendment #1 to Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated August 13, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.38	Letter Agreement Amendment between the Registrant and Biogen Idec International Holding Ltd dated January 27, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.39	Amendment No. 3 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated July 10, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.40	Amendment #4 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated April 10, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.41	Amendment #5 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated June 27, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.42	Exclusive License Agreement between the Registrant and the University of Massachusetts dated January 14, 2010, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.43	Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated October 26, 2011, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.44	Amendment to Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated March 14, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.45	Amendment #1 to the Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated December 15, 2014, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.46	Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 22, 2014. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.47	Amendment No.2 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated October 15, 2014, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.48	Strategic Collaboration Agreement between the Registrant and AstraZeneca AB dated July 31, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.49	Amendment #6 to Research, Development and License Agreement between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated September 2, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.50	Amendment Number One to the Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated July 13, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.51	License Agreement between the Registrant and Bayer Pharma AG dated May 1, 2015. Portions of this exhibit have been omitted and separately filed with the SEC, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.52	Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated January 8, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.53	Amendment #1 to HTT Research, Development, Option and License Agreement between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. dated January 9, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.54	Amendment No.3 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated January 18, 2016, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.55	Amendment #7 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated March 4, 2016, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.56	First Amendment to Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 21, 2016. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.57	Letter Agreement between the Registrant and Biogen MA Inc. dated October 28, 2016, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.58	Guaranty between the Registrant and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.59	Environmental Indemnity Agreement among the Registrant, Ionis Gazelle, LLC and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.60*	Registrant's Severance Benefit Plan and Summary Plan Description dated October 18, 2018, filed as an exhibit to the Registrant's Current Report on form 8-K filed October 18, 2018 and incorporated herein by reference.
10.61	Third Amended and Restated Strategic Advisory Services Agreement by and between the Registrant and B. Lynne Parshall, dated February 22, 2021
10.62	Development, Commercialization, Collaboration, and License Agreement by and between the Registrant and Akcea Therapeutics, Inc., dated March 14, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 and incorporated herein by reference.
10.63	Amended and Restated Services Agreement by and between the Registrant and Akcea Therapeutics, Inc., dated March 14, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 and incorporated herein by reference.
10.64	New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated April 19, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.65	Stock Purchase Agreement by and between the Registrant and Biogen MA Inc., dated April 19, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2018 and incorporated herein by reference.
10.66	Second Amendment to Research, Collaboration, Option and License Agreement by and between the Registrant and Janssen Biotech Inc., dated August 7, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.67	Factor B Development Collaboration, Option and License Agreement by and between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., dated October 9, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.68	Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated October 17, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.69	Amendment #1 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.70	Amendment #4 to the Collaboration, License and Development Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.71	Amendment #1 to Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated May 2, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2019 and incorporated herein by reference.

10.72	Amendment #1 to the New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen MA Inc., dated August 16, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.73	Amendment #8 to the Research, Development and License Agreement between the Registrant, Glaxo Group Limited and Glaxosmithkline Intellectual Property Development Limited, dated July 29, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.74	Consent to Collateral Addition and Amendment to Loan Documents between the Registrant, Ionis Gazelle, LLC, Wells Fargo Bank, National Association, as Trustee for the Benefit of the Registered Holders of UBS Commercial Mortgage Trust 2017-C3, Commercial Mortgage Pass-Through Certificates, Series 2017-C3, dated August 1, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference.
10.75	License Agreement by and among Akcea Therapeutics, Inc. and Pfizer Inc. dated October 4, 2019, filed as an exhibit to Akcea Therapeutics, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2019 and incorporated herein by reference.
10.76	Letter Agreement between the Registrant, Akcea Therapeutics, Inc., and Pfizer Inc., dated October 4, 2019, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.77	Side Letter dated June 11, 2020 to the Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated October 17, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.78	Amendment No. 2 dated April 30, 2020 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB dated July 31, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.79	Amendment No. 3 dated December 17, 2020 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB dated July 31, 2015. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.80	Strategic Advisory Services Agreement by and between the Registrant and Stanley T. Crooke, dated December 17, 2020.
10.81	Side Letter dated December 31, 2020 to the New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated April 19, 2018. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.

21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney – Included on the signature page of this Annual Report on Form 10-K.
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1+	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2020, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of comprehensive income (loss), (iv) consolidated statements of stockholders' equity (v) consolidated statements of cash flows, and (vi) notes to consolidated financial statements (detail tagged)
104	Cover Page Interactive Data File (formatted in iXBRL and included in exhibit 101)

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

\+ This certification is deemed not filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 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 24th day of February, 2021.

IONIS PHARMACEUTICALS, INC.

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

POWER OF ATTORNEY

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

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

Signatures	Title	Date
/s/ BRETT P. MONIA Brett P. MONIA, Ph.D.	Director and Chief Executive Officer (Principal executive officer)	February 24, 2021
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	February 24, 2021
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Executive Chairman of the Board	February 24, 2021
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director and Senior Strategic Advisor	February 24, 2021
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 24, 2021
/s/ BREAUX CASTLEMAN Breaux Castleman	Director	February 24, 2021
/s/ MICHAEL HAYDEN Michael Hayden, CM OBC MB ChB PhD FRCP(C) FRSC	Director	February 24, 2021
/s/ JOAN E. HERMAN Joan E. Herman	Director	February 24, 2021
/s/ JOSEPH KLEIN Joseph Klein, III	Director	February 24, 2021
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Director	February 24, 2021
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	February 24, 2021
/s/ PETER N. REIKES Peter N. Reikes	Director	February 24, 2021
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	February 24, 2021

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

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

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures include examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

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

Realizability of Deferred Tax Assets

Description of the Matter

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

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

How We Addressed the Matter in Our Audit

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

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

/s/ Ernst & Young LLP

We have served as the Company's auditor since 1989

San Diego, California
February 24, 2021

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

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

See accompanying notes.

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

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

See accompanying notes.

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

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

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2020, 2019 and 2018
(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, 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 gain, net of tax	—	—	—	6,633	—	6,633	—	6,633
Foreign currency translation	—	—	—	93	—	93	—	93
Issuance of common stock in connection with employee stock plans	3,100	3	119,654	—	—	119,657	—	119,657
1 percent convertible senior notes retirement, equity portion, net of tax	—	—	(77,331)	—	—	(77,331)	—	(77,331)
0.125 percent convertible senior notes, equity portion, net of issuance costs and tax	—	—	81,877	—	—	81,877	—	81,877
Issuance of warrants	—	—	56,110	—	—	56,110	—	56,110
Purchase of note hedges, net of tax	—	—	(85,860)	—	—	(85,860)	—	(85,860)
Repurchases and retirements of common stock	(535)	(1)	—	—	(34,387)	(34,388)	—	(34,388)
Stock-based compensation expense	—	—	146,574	—	—	146,574	—	146,574
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(154)	—	(19,242)	—	—	(19,242)	—	(19,242)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(65,254)	—	—	(65,254)	74,372	9,118
Balance at December 31, 2019	140,340	$ 140	$ 2,203,778	$ (25,290)	$ (707,534)	$ 1,471,094	$ 213,453	$ 1,684,547
Net loss	—	—	—	—	(451,286)	(451,286)	—	(451,286)
Change in unrealized gains, net of tax	—	—	—	3,729	—	3,729	—	3,729
Foreign currency translation	—	—	—	617	—	617	—	617
Issuance of common stock in connection	1,721	1	52,033	—	—	52,034	—	52,034

with employee stock plans								
Purchase of noncontrolling interest of Akcea Therapeutics, Inc., including cash payments for cancellation of Akcea Therapeutics, Inc. equity awards	—	—	(324,022)	301	—	(323,721)	(220,965)	(544,686)
Repurchases and retirement of common stock	(1,478)	(1)	—	—	(90,548)	(90,549)	—	(90,549)
Stock-based compensation expense	—	—	230,117	—	—	230,117	—	230,117
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(217)	—	(13,410)	—	—	(13,410)	—	(13,410)
Deferred tax liability adjustment due to purchase of noncontrolling interest of Akcea Therapeutics, Inc.	—	—	7,714	—	—	7,714	—	7,714
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(42,564)	(428)	—	(42,992)	7,512	(35,480)
Balance at December 31, 2020	140,366	$ 140	$ 2,113,646	$ (21,071)	$ (1,249,368)	$ 843,347	$ —	$ 843,347

See accompanying notes.

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

	Year Ended December 31,		
	2020	**2019**	**2018**
Operating activities:			
Net income (loss)	$ (486,766)	$ 303,262	$ 214,985
Adjustments to reconcile net income (loss) to net cash provided by operating activities:			
Depreciation	13,365	12,540	10,706
Amortization of right-of-use operating lease assets	1,731	1,542	—
Amortization of patents	2,064	1,912	1,822
Amortization of premium (discount) on investments, net	11,521	(7,485)	(1,013)
Amortization of debt issuance costs	2,578	1,942	1,810
Amortization of convertible senior notes discount	36,157	37,338	33,363
Stock-based compensation expense	230,117	146,574	131,312
Loss on early retirement of debt	—	21,865	—
(Gain) loss on investments	(16,540)	(192)	210
Deferred income taxes, including changes in valuation allowance	313,272	(7,096)	(290,516)
Non-cash losses related to patents	1,948	2,226	802
Changes in operating assets and liabilities:			
Contracts receivable	(13,170)	(47,674)	47,595
Inventories	(1,261)	(5,411)	1,400
Other current and long-term assets	(9,975)	(44,659)	(29,348)
Long-term income tax receivable	—	8,418	(223)
Accounts payable	(2,755)	(16,343)	(655)
Income taxes	(31,279)	31,656	(710)
Accrued compensation	28,371	8,089	4,117
Accrued liabilities and deferred rent	32,424	16,406	(17,005)
Deferred contract revenue	(75,910)	(119,283)	494,254
Net cash provided by operating activities	35,892	345,627	602,906
Investing activities:			
Purchases of short-term investments	(1,570,410)	(1,946,726)	(1,794,735)
Proceeds from the sale of short-term investments	1,885,935	1,951,734	882,824
Purchases of property, plant and equipment	(35,120)	(30,905)	(13,608)
Acquisition of licenses and other assets, net	(5,928)	(5,377)	(4,044)
Purchase of strategic investments	—	(10,000)	—
Net cash provided by (used in) investing activities	274,477	(41,274)	(929,563)
Financing activities:			
Proceeds from equity, net	52,036	119,657	27,900
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(13,411)	(19,242)	—
Proceeds from the issuance of 0.125 percent convertible senior notes	—	109,500	—
0.125 percent convertible senior notes issuance costs	—	(10,428)	—
Proceeds from issuance of warrants	—	56,110	—
Purchase of note hedges	—	(108,684)	—
Repurchases and retirements of common stock	(90,548)	(34,392)	—
Purchase of noncontrolling interest of Akcea Therapeutics, Inc., including cash payments for cancellation of Akcea Therapeutics, Inc. equity awards	(544,686)	—	—
Principal payments on line of credit	—	(12,500)	—
Proceeds from the issuance of common stock to Biogen	—	—	447,965
Net cash (used in) provided by financing activities	(596,609)	100,021	475,865
Effects of exchange rates on cash	617	93	(18)
Net (decrease) increase in cash and cash equivalents	(285,623)	404,467	149,190
Cash and cash equivalents at beginning of year	683,287	278,820	129,630
Cash and cash equivalents at end of year	$ 397,664	$ 683,287	$ 278,820

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

	Year Ended December 31,		
	2020	**2019**	**2018**
Supplemental disclosures of cash flow information:			
Interest paid	$ 6,247	$ 9,870	$ 9,592
Income taxes paid	$ 25,855	$ 9,041	$ —
Supplemental disclosures of non-cash investing and financing activities:			
Right-of-use assets obtained in exchange for lease liabilities	$ 2,149	$ 14,178	$ —
Amounts accrued for capital and patent expenditures	$ 4,059	$ 3,126	$ 4,428
Purchases of property, plant and equipment included in long-term obligations	$ —	$ —	$ 3,350
0.125 percent convertible senior notes principal issued related to our December 2019 debt exchange/issuance	$ —	$ 439,326	$ —
1 percent convertible senior notes principal extinguished related to our December 2019 debt exchange	$ —	$ 375,590	$ —

See accompanying notes.

1. Organization and Significant Accounting Policies

Basis of Presentation

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

Organization and Business Activity

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

Basic and Diluted Net Income (Loss) per Share

Basic net income (loss) per share

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

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

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

Year Ended December 31, 2020	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Loss Per Share Calculation
Akcea's net loss in the pre-acquisition period attributable to our ownership	77,095	$ (1.45)	$ (111,775)
Akcea's net loss in the post-acquisition period attributable to our ownership			(85,987)
Akcea's total net loss attributable to our ownership			$ (197,762)
Ionis' stand-alone net loss			(253,725)
Net loss available to Ionis common stockholders			$ (451,487)
Weighted average shares outstanding			139,612
Basic net loss per share			$ (3.23)

Year Ended December 31, 2019	Weighted Average Shares Owned in Akcea	Akcea's Net Income Per Share	Basic Net Income Per Share Calculation
Common shares	70,100	$ 0.49	$ 34,073
Akcea's net income attributable to our ownership			$ 34,073
Ionis' stand-alone net income			262,490
Net income available to Ionis common stockholders			$ 296,563
Weighted average shares outstanding			139,998
Basic net income per share			$ 2.12

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

Diluted net income per share

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

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

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

Year Ended December 31, 2019	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 296,563	139,998	$ 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 ESPP	—	18	
	$ 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 ESPP	—	6	
	$ 276,868	134,056	$ 2.07

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

Revenue Recognition

Our Revenue Sources

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

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

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

Commercial Revenue: Product sales, net

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

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

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

Research and development revenue under collaborative agreements

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

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

Steps to Recognize Revenue

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

1. Identify the contract

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

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

2. Identify the performance obligations

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

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

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

3. Determine the transaction price

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

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

4. Allocate the transaction price

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

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

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

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

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

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

5. Recognize revenue

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

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

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

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

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

Commercial Revenue: Product sales, net

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

Reserves for Product sales

We record product sales at our net sales price, or transaction price. We include in our transaction price estimated reserves for discounts, returns, chargebacks, rebates and other allowances that we offer within contracts between us and our customers, wholesalers, health care providers and other indirect customers. We estimate our reserves using the amounts we have earned or what we can claim on the associated sales. We classify our reserves as a reduction of accounts receivable when we are not required to make a payment or as a current liability when we are required to make a payment. In certain cases, our estimates include a range of possible outcomes that are probability weighted for relevant factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. Overall, our reserves reflect our best estimates under the terms of our respective contracts. When calculating our reserves and related product sales, we only recognize amounts to the extent that we consider it probable that we would not have to reverse in a future period a significant amount of the cumulative sales we previously recognized. The actual amounts we receive may ultimately differ from our reserve estimates. If actual amounts in the future vary from our estimates, we will adjust these estimates, which would affect our net product sales in the respective period.

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

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

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

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

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

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

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

Research and development revenue under collaboration agreements:

Upfront payments

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

Milestone payments

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

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

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

License fees

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

Sublicense fees

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

Amendments to Agreements

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

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

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

For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. As part of the agreement, Bayer paid us a $100 million upfront payment. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis and for providing an initial supply of API. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. As part of the 2017 amendment, Bayer paid us $75 million. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$ and IONIS-FXI-L$_{Rx}$. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of IONIS-FXI-L$_{Rx}$, to provide R&D services and to deliver API. We allocated the $75 million transaction price to these performance obligations. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, in our audited financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2019 for further discussion of the Bayer collaboration.

Multiple agreements

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

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

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

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

Contracts Receivable

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

Unbilled SPINRAZA Royalties

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

Deferred Revenue

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

Cost of Products Sold

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

Research, Development and Patent Expenses

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

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

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

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

Year Ending December 31,	Amortization (in millions)
2021	$ 2.1
2022	$ 2.0
2023	$ 1.9
2024	$ 1.7
2025	$ 1.6

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

Accrued Liabilities

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

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

Noncontrolling Interest in Akcea Therapeutics, Inc.

Since Akcea's IPO in July 2017 and prior to the Akcea Acquisition in October 2020, the shares of Akcea's common stock third parties owned represented an interest in Akcea's equity that we did not control. During this period our ownership ranged from 68 percent to 77 percent. However, as we maintained overall control of Akcea through our voting interest, we reflected the assets, liabilities and results of operations of Akcea in our consolidated financial statements. Since Akcea's IPO in July 2017 and through the closing of the Akcea Acquisition, we reflected the noncontrolling interest attributable to other owners of Akcea's common stock on a separate line on our statement of operations and a separate line within stockholders' equity in our consolidated balance sheet. In addition, through the closing of the Akcea Acquisition, we recorded a noncontrolling interest adjustment to account for the stock options Akcea granted, which if exercised, would have diluted our ownership in Akcea. This adjustment was a reclassification within stockholders' equity from additional paid-in capital to noncontrolling interest in Akcea equal to the amount of stock-based compensation expense Akcea had recognized. Additionally, we reflected changes in our ownership percentage in our financial statements as an adjustment to noncontrolling interest in the period the change occurred.

Concentration of Credit Risk

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

Cash, Cash Equivalents and Investments

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

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

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

Inventory Valuation

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

We obtained the first regulatory approval for TEGSEDI in July 2018 and for WAYLIVRA in May 2019. At December 31, 2020, our physical inventory for TEGSEDI and WAYLIVRA included API that we produced prior to when we obtained regulatory approval. As such, this API has no cost basis as we had previously expensed the costs as R&D expenses.

We review our inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value based on forecasted demand compared to quantities on hand. We consider several factors in estimating the net realizable value, including shelf life of our inventory, alternative uses for our medicines in development and historical write-offs. We recorded an insignificant amount of inventory write-offs during the years ended December 31, 2020 and 2019. We did not record any inventory write-offs for the year ended December 31, 2018.

Our inventory consisted of the following (in thousands):

	December 31,	
	2020	2019
Raw materials:		
Raw materials- clinical	$ 9,206	$ 9,363
Raw materials- commercial	7,502	6,520
Total raw materials	16,708	15,883
Work in process	2,252	2,039
Finished goods	3,005	258
Total inventory	$ 21,965	$ 18,180

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,	
		2020	2019
Computer software, laboratory, manufacturing and other equipment	3 to 10	$ 68,990	$ 60,965
Building, building improvements and building systems	15 to 40	137,879	119,830
Land improvements	20	8,391	2,853
Leasehold improvements	5 to 15	17,263	13,600
Furniture and fixtures	5 to 10	12,871	7,354
		245,394	204,602
Less accumulated depreciation		(87,379)	(74,013)
		158,015	130,589
Land		23,062	23,062
Total		$ 181,077	$ 153,651

We depreciate our leasehold improvements using the shorter of the estimated useful life or remaining lease term.

Fair Value of Financial Instruments

We have estimated the fair value of our financial instruments. The amounts reported for cash, accounts receivable, accounts payable and accrued expenses approximate the fair value because of their short maturities. We report our investment securities at their estimated fair value based on quoted market prices for identical or similar instruments.

Leases

We determine if an arrangement contains a lease at inception. We currently only have operating leases. We recognize a right-of-use operating lease asset and associated short- and long-term operating lease liability on our consolidated balance sheet for operating leases greater than one year. Our right-of-use assets represent our right to use an underlying asset for the lease term and our lease liabilities represent our obligation to make lease payments arising from the lease arrangement. We recognize our right-of-use operating lease assets and lease liabilities based on the present value of the future minimum lease payments we will pay over the lease term. We determine the lease term at the inception of each lease, and in certain cases our lease term could include renewal options if we concluded we were reasonably certain that we will exercise the renewal option. When we exercise a lease option that was not previously included in the initial lease term, we reassess our right-of-use asset and lease liabilities for the new lease term.

As our current leases do not provide an interest rate implicit in the lease, we used our incremental borrowing rate, based on the information available on the date we adopted Topic 842 (January 2019), as of the lease inception date or at the lease option extension date in determining the present value of future payments. We recognize rent expense for our minimum lease payments on a straight-line basis over the expected term of our lease. We recognize period expenses, such as common area maintenance expenses, in the period we incur the expense.

Long-Lived Assets

We evaluate long-lived assets, which include property, plant and equipment and patent costs, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets. We recorded charges of $1.9 million, $2.2 million and $0.8 million for the years ended December 31, 2020, 2019 and 2018, respectively, related to the write-down of patents.

Use of Estimates

The preparation of consolidated financial statements in conformity with accounting principles generally accepted in the U.S. requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Stock-Based Compensation Expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, RSUs, and stock purchase rights under our ESPP based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise in subsequent periods if actual forfeitures differ from those estimates.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. On the grant date, we use our stock price and assumptions regarding a number of variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on historical exercise patterns.

We recognize compensation expense for option awards and RSUs using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), we recognize compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

The fair value of RSUs is based on the market price of our common stock on the date of grant. The RSUs we have granted vest annually over a four-year period. RSUs granted after June 2020 to our board of directors vest annually.

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

Accumulated Other Comprehensive Loss

Accumulated other comprehensive loss is comprised of unrealized gains and losses on investments, net of taxes and currency translation adjustments. The following table summarizes changes in accumulated other comprehensive loss for the years ended December 31, 2020, 2019 and 2018 (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Beginning balance accumulated other comprehensive loss	$ (25,290)	$ (32,016)	$ (31,759)
Unrealized gains (losses) on securities, net of tax (1)	3,729	6,633	(280)
Currency translation adjustment	617	93	23
Adjustments to other comprehensive loss from purchase of noncontrolling interest of Akcea Therapeutics, Inc.	(127)	—	—
Net other comprehensive loss for the period	4,219	6,726	(257)
Ending balance accumulated other comprehensive loss	$ (21,071)	$ (25,290)	$ (32,016)

(1) We did not have tax expense included in our other comprehensive loss for the year ended December 31, 2020. For the years ended December 31, 2019 and 2018, we had a tax benefit $1.4 million and $0.3 million included in other comprehensive loss respectively.

Convertible Debt

At issuance, we accounted for our convertible debt instruments, including our 0.125 percent senior convertible notes, or 0.125% Notes, and 1 percent senior convertible notes, or 1% Notes, that may be settled in cash upon conversion (including partial cash settlement) by separating the liability and equity components of the instruments in a manner that reflects our nonconvertible debt borrowing rate on the date the notes were issued. In reviewing debt issuances, we were not able to identify any comparable companies that issued non-convertible debt instruments at the time of the issuance of the convertible notes. Therefore, we estimated the fair value of the liability component of our notes by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities.

We assigned a value to the debt component of our convertible notes equal to the estimated fair value of similar debt instruments without the conversion feature, which resulted in us recording our debt at a discount. We are amortizing our debt issuance costs and debt discount over the life of the convertible notes as additional non-cash interest expense utilizing the effective interest method. For additional information, see Note 3, *Long-Term Obligations and Commitments*.

The 1% Notes mature in November 2021. Therefore, as of December 31, 2020, we classified the liability component of the 1% Notes as a current liability on our consolidated balance sheet.

In August 2020, the FASB issued guidance simplifying the accounting for convertible debt instruments. See the section titled “Impact of Recently Issued Accounting Standards” below for details.

Call Spread

In conjunction with the issuance of our 0.125% Notes, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants. We account for the note hedges and warrants as separate freestanding financial instruments and treat each instrument as a separate unit of accounting. We determined that the note hedges and warrants do not meet the definition of a liability using the guidance contained in ASC Topic 480, therefore we account for the note hedges and warrants using the Derivatives and Hedging – Contracts in Entity’s Own Equity accounting guidance contained in ASC Topic 815. We determined that the note hedges and warrants meet the definition of a derivative, are indexed to our stock and meet the criteria to be classified in shareholders’ equity. We recorded the aggregate amount paid for the note hedges and the aggregate amount received for the warrants as additional paid-in capital in our consolidated balance sheet. We reassess our ability to continue to classify the note hedges and warrants in shareholders’ equity at each reporting period.

Segment Information

Through 2020, we had two operating segments, our Ionis Core segment and Akcea Therapeutics. Akcea was focused on developing and commercializing medicines to treat patients with serious and rare diseases. We have provided segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviewed to assess operating performance and to make operating decisions through 2020. We allocated a portion of Ionis’ development, R&D support and general and administrative expenses to Akcea for work Ionis performed on behalf of Akcea and we billed Akcea for these expenses.

Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in equity securities in publicly held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. We classify most of our securities as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices.

The following tables present the major security types we held at December 31, 2020 and 2019 that we regularly measure and carry at fair value. At December 31, 2019, our ProQR investment was subject to trading restrictions until the fourth quarter of 2020, as a result we included a lack of marketability discount in valuing this investment, which is a Level 3 input. As of December 31, 2020, our ProQR investment was no longer subject to trading restrictions. As of December 31, 2020, we did not have any investments which we valued using Level 3 inputs. The following tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At December 31, 2020	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 221,125	$ 221,125	$ —
Corporate debt securities (2)	846,315	—	846,315
Debt securities issued by U.S. government agencies (4)	174,861	—	174,861
Debt securities issued by the U.S. Treasury (3)	358,497	358,497	—
Debt securities issued by states of the U.S. and political subdivisions of the states (4)	136,309	—	136,309
Other municipal debt securities (4)	6,225	—	6,225
Investment in ProQR Therapeutics N.V. (5)	2,031	2,031	—
Total	$ 1,745,363	$ 581,653	$ 1,163,710

	At December 31, 2019	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 418,406	$ 418,406	$ —	$ —
Corporate debt securities (6)	1,102,568	—	1,102,568	—
Debt securities issued by U.S. government agencies (7)	329,404	—	329,404	—
Debt securities issued by the U.S. Treasury (4)	363,694	363,694	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (4)	40,407	—	40,407	—
Investment in ProQR Therapeutics N.V. (5)	4,506	—	—	4,506
Total	$ 2,258,985	$ 782,100	$ 1,472,379	$ 4,506

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

(2) $10.0 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(3) $17.5 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(4) Included in short-term investments.

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

(6) $19.0 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(7) $0.8 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

Income Taxes

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in our financial statements or tax returns. In addition, deferred tax assets are recorded for the future benefit of utilizing net operating losses and research and development credit carryforwards. We record a valuation allowance when necessary to reduce our net deferred tax assets to the amount expected to be realized.

We apply the authoritative accounting guidance prescribing a threshold and measurement attribute for the financial recognition and measurement of a tax position taken or expected to be taken in a tax return. We recognize liabilities for uncertain tax positions based on a two-step process. The first step is to evaluate the tax position for recognition by determining if the weight of available evidence indicates that it is more likely than not that the position will be sustained on audit, including resolution of related appeals or litigation processes, if any. The second step requires us to estimate and measure the tax benefit as the largest amount that is more than 50 percent likely to be realized upon ultimate settlement.

We are required to use significant judgment in evaluating our uncertain tax positions and determining our provision for income taxes. Although we believe our reserves are reasonable, no assurance can be given that the final tax outcome of these matters will not be different from that which is reflected in our historical income tax provisions and accruals. We adjust these reserves for changing facts and circumstances, such as the closing of a tax audit or the refinement of an estimate. To the extent that the final tax outcome of these matters is different than the amounts recorded, such differences may impact the provision for income taxes in the period in which such determination is made.

We are also required to use significant judgment in determining any valuation allowance recorded against our deferred tax assets. In assessing the need for a valuation allowance, we consider all available evidence, including scheduled reversal of deferred tax liabilities, past operating results, the feasibility of tax planning strategies and estimates of future taxable income. We base our estimates of future taxable income on assumptions that are consistent with our plans. The assumptions we use represent our best estimates and involve inherent uncertainties and the application of our judgment. Should actual amounts differ from our estimates, the amount of our tax expense and liabilities we recognize could be materially impacted. We record a valuation allowance to reduce the balance of our net deferred tax assets to the amount we believe is more-likely-than-not to be realized.

We do not provide for a U.S. income tax liability and foreign withholding taxes on undistributed foreign earnings of our foreign subsidiaries.

Impact of Recently Issued Accounting Standards

In June 2016, the FASB issued guidance that changes the measurement of credit losses for most financial assets and certain other instruments. If we have credit losses, this updated guidance requires us to record allowances for these instruments under a new expected credit loss model. This model requires us to estimate the expected credit loss of an instrument over its lifetime, which represents the portion of the amortized cost basis we do not expect to collect. The new guidance requires us to remeasure our allowance in each reporting period we have credit losses. We adopted this new guidance on January 1, 2020. This guidance did not have an impact on our consolidated financial statements.

In August 2018, the FASB issued clarifying guidance on how to account for implementation costs related to cloud-servicing arrangements. The guidance states that if these fees qualify to be capitalized and amortized over the service period, they need to be expensed in the same line item as the service expense and recognized in the same balance sheet category. The update can be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. We adopted this guidance on January 1, 2020 on a prospective basis. This guidance did not have an impact on our consolidated financial statements.

In November 2018, the FASB issued clarifying guidance of the interaction between the collaboration accounting guidance and the new revenue recognition guidance we adopted on January 1, 2018 (Topic 606). Below is the clarifying guidance and how we implemented it (in italics):

1) When a participant is considered a customer in a collaborative arrangement, all of the associated accounting under Topic 606 should be applied.
    - *We are applying all of the associated accounting under Topic 606 when we determine a participant in a collaborative arrangement is a customer.*
2) Adds "unit of account" concept to collaboration accounting guidance to align with Topic 606. The "unit of account" concept is used to determine if revenue is recognized or if a contra expense is recognized from consideration received under a collaboration.
    - *We use the "unit of account" concept when we receive consideration under a collaborative arrangement to determine when we recognize revenue or a contra expense.*
3) The clarifying guidance precludes us from recognizing revenue under Topic 606 when we determine a transaction with a collaborative partner is not a customer and is not directly related to the sales to third parties.
    - *When we conclude a collaboration partner is not a customer and is not directly related to the sales to third parties, we do not recognize revenue for the transaction.*

We adopted this new guidance on January 1, 2020. This guidance did not have any impact on our consolidated financial statements.

In August 2020, the FASB issued guidance which simplifies the accounting for convertible instruments, amends the guidance on derivative scope exceptions for contracts in an entity's own equity, and modifies the guidance on diluted earnings per share calculations as a result of these changes. Under our current outstanding convertible debt arrangements, we anticipate the following impacts:

1) We will no longer separate our existing convertible debt into liability and equity components. Therefore, we will no longer recognize a debt discount for the value of the conversion option, instead we will record the face value of the convertible debt as a liability on our consolidated balance sheet;
2) We will record cash interest expense plus amortization of debt issuance costs to interest expense. Since we will not recognize a debt discount, we will no longer record the amortization of a debt discount to interest expense; and
3) We do not expect our EPS calculation to not change under this update. We plan to continue to use the if-converted method to calculate diluted earnings per share.

We plan to adopt this guidance in the first quarter of 2021 under the full retrospective approach, meaning we will apply the guidance to all periods presented beginning in the first quarter of 2021.

2. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2020:

One year or less	73%
After one year but within two years	18%
After two years but within three and a half years	9%
Total	100%

As illustrated above, at December 31, 2020, 91 percent of our available-for-sale securities had a maturity of less than two years.

All of our available-for-sale securities are available to us for use in our current operations. As a result, we categorize all of these securities as current assets even though the stated maturity of some individual securities may be one year or more beyond the balance sheet date.

At December 31, 2020, we had an ownership interest of less than 20 percent in seven private companies and two public companies with which we conduct business. The privately-held companies are Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd. The publicly traded companies are ATL and ProQR.

The following is a summary of our investments (in thousands):

December 31, 2020	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (2)	$ 514,182	$ 2,194	$ (41)	$ 516,335
Debt securities issued by U.S. government agencies	94,234	354	(2)	94,586
Debt securities issued by the U.S. Treasury (2)	307,576	233	(9)	307,800
Debt securities issued by states of the U.S. and political subdivisions of the states	104,271	196	(12)	104,455
Other municipal debt securities	5,191	—	(7)	5,184
Total securities with a maturity of one year or less	1,025,454	2,977	(71)	1,028,360
Corporate debt securities	325,079	4,941	(40)	329,980
Debt securities issued by U.S. government agencies	80,099	185	(9)	80,275
Debt securities issued by the U.S. Treasury	50,318	383	(4)	50,697
Debt securities issued by states of the U.S. and political subdivisions of the states	31,779	91	(16)	31,854
Other municipal debt securities	1,041	—	—	1,041
Total securities with a maturity of more than one year	488,316	5,600	(69)	493,847
Total available-for-sale securities	$ 1,513,770	$ 8,577	$ (140)	$ 1,522,207
Equity securities:				
Total equity securities included in other current assets (3)	$ 4,712	$ —	$ (2,681)	$ 2,031
Total equity securities included in deposits and other assets (4)	15,062	15,938	—	31,000
Total equity securities	$ 19,774	$ 15,938	$ (2,681)	$ 33,031
Total available-for-sale and equity securities	$ 1,533,544	$ 24,515	$ (2,821)	$ 1,555,238

December 31, 2019	Cost (1)	Gross Unrealized 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

(1) We hold our available-for-sale securities at amortized cost.

(2) Includes investments classified as cash equivalents on our consolidated balance sheet.

(3) Our equity securities included in other current assets consisted of our investments in publicly traded companies. We recognize publicly traded equity securities at fair value.

(4) Our equity securities included in deposits and other assets consisted of our investments in privately held companies. We recognize our private company equity securities at cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer on our consolidated balance sheet.

The following is a summary of our investments we considered to be temporarily impaired at December 31, 2020 (in thousands). All of these investments have less than 12 months of temporary impairment. We believe that the decline in value of these securities is temporary and is primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold our debt securities to maturity. Therefore, we anticipate full recovery of our debt securities' amortized cost basis at maturity.

	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	54	$ 121,162	$ (81)
Debt securities issued by U.S. government agencies	2	29,988	(11)
Debt securities issued by the U.S. Treasury	8	76,941	(13)
Debt securities issued by states of the U.S. and political subdivisions of the states	160	49,832	(28)
Other municipal debt securities	2	6,225	(7)
Total temporarily impaired securities	226	$ 284,148	$ (140)

3. Long-Term Obligations and Commitments

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

	December 31,	
	2020	2019
0.125 percent convertible senior notes	$ 455,719	$ 434,711
1 percent convertible senior notes (1)	293,161	275,333
Long-term mortgage debt	59,984	59,913
Leases and other obligations	30,710	17,569
Total	$ 839,574	$ 787,526
Less: current portion (1)	(300,462)	(2,026)
Total Long-Term Obligations	$ 539,112	$ 785,500

(1) We classified the carrying value of our 1% Notes as a current liability on our consolidated balance sheet at December 31, 2020 because it matures in November 2021.

Convertible Notes and Call Spread

0.125 Percent Convertible Senior Notes

In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange $375.6 million of our 1% Notes for $439.3 million of our 0.125% Notes, and to issue $109.5 million of our 0.125% Notes. We completed this exchange to reduce our cash interest payments, increase our conversion price and extend our maturity for a large portion of our debt. Additionally, in conjunction with the December 2019 exchange, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the effective conversion price even further.

Interest is payable semi-annually on June 15 and December 15 of each year for the 0.125% Notes. The 0.125% Notes are convertible at the option of the note holders prior to August 1, 2024 only under certain conditions. On or after August 1, 2024, the 0.125% Notes are initially convertible into approximately 6.6 million shares of common stock at a conversion price of approximately $83.28 per share. We will settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the 0.125% Notes prior to maturity, and no sinking fund is provided for them. If we undergo a fundamental change, holders may require us to purchase for cash all or any portion of their 0.125% Notes at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest to, but excluding, the fundamental change purchase date.

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

	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, 2020 and 2019:

	December 31,	
	2020	2019
Fair value of outstanding notes	$ 564.9	$ 558.7
Principal amount of convertible notes outstanding	$ 548.8	$ 548.8
Unamortized portion of debt discount	$ 86.0	$ 105.2
Long-term debt	$ 455.7	$ 434.7
Carrying value of equity component	$ 105.8	$ 105.8

Call Spread

Additionally, in conjunction with the December 2019 exchange, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the conversion price even further. The call spread cost us $52.6 million, of which $108.7 million was for the note hedge purchase, offset by $56.1 million we received for selling the warrants. We increased our effective conversion price to $123.38 with the same number of underlying shares as our 0.125% Notes. We accounted for our call spread transactions using the Derivatives and Hedging – Contracts in Entity's Own Equity accounting guidance contained in Topic 815. We determined that the call spread transactions meet the definition of a derivative, are indexed to our stock and meet the criteria to be classified in shareholders' equity.

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

We recorded the aggregate amount paid for the note hedges and the aggregate amount received for the warrants in additional paid-in capital in our consolidated balance sheet. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period. We excluded shares under the note hedges from our calculation of diluted earnings per share as they were antidilutive. We will include the shares issuable under the warrants in our calculation of diluted earnings per share when the average market price per share of our common stock for the reporting period exceeds the strike price of the warrants.

1 Percent Convertible Senior Notes

In November 2014, we completed a $500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1% Notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes, or 2¾%% Notes. In December 2016, we issued an additional $185.5 million of 1% Notes in exchange for the redemption of $61.1 million of our 2¾%% Notes. In December 2019, we exchanged a portion of our 1% Notes for 0.125% Notes. As a result, the principal balance of 1% Notes was $309.9 million. Additionally, we recorded a $21.9 million non-cash loss on early retirement of debt, reflecting the early retirement of a significant portion of our 1% Notes in December 2019.

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

	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, 2020 and 2019:

	December 31,	
	2020	2019
Fair value of outstanding notes	$ 338.5	$ 354.8
Principal amount of convertible notes outstanding	$ 309.9	$ 309.9
Unamortized portion of debt discount	$ 15.8	$ 32.8
Current/long-term debt	$ 293.2	$ 275.3
Carrying value of equity component	$ 33.5	$ 33.5

We account for our convertible notes using an accounting standard that requires us to assign a value to our convertible debt equal to the estimated fair value of similar debt instruments without the conversion feature and to record the remaining portion in equity. As a result, we recorded our convertible notes at a discount, which we are amortizing as additional non-cash interest expense over the expected life of the respective debt. We determined our nonconvertible debt borrowing rate using a combination of the present value of the debt's cash flows and a Black-Scholes valuation model. The following table summarizes the nonconvertible borrowing rate, effective interest rate and amortization period of our debt discount for our convertible notes:

	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, 2020, 2019 and 2018 included $38.7 million, $39.3 million and $35.2 million, respectively, of non-cash interest expense related to the amortization of the debt discount and debt issuance costs for our convertible notes.

Financing Arrangements

Line of Credit Arrangement

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley, which we amended in February 2016. Under the amended credit agreement, Morgan Stanley provided a maximum of $30 million of revolving credit for general working capital purposes. During the third quarter of 2019, we paid off our total outstanding borrowings of $12.5 million under the agreement and subsequently terminated the agreement.

Research and Development and Manufacturing Facilities

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

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2020 are as follows (in thousands):

2021	$ 329,189
2022	3,495
2023	4,180
2024	553,006
2025	3,494
Thereafter	60,933
Subtotal	$ 954,297
Less: current portion	(300,462)
Less: fixed and determinable interest	(21,758)
Less: unamortized portion of debt discount	(101,820)
Less: debt issuance costs	(8,455)
Plus: lease liabilities	17,310
Total long-term debt	$ 539,112

Operating Leases

Carlsbad Leases

We lease a facility adjacent to our manufacturing facility that has laboratory and office space that we use to support our manufacturing facility. We lease this space under a non-cancelable operating lease. In May 2020, we exercised our option to extend our lease, extending our lease term from June 2021 to August 2026. We have one remaining option to extend the lease for an additional five-year period.

We also lease additional office spaces in Carlsbad. We lease these spaces under non-cancelable operating leases with initial terms ending in 2023 with options to extend each of the leases for one five-year period.

Boston Lease

We entered into an operating lease agreement for office space located in Boston, Massachusetts in the second quarter of 2018. The lease commencement date was in August 2018 and we took occupancy in September 2018. We are leasing this space under a non-cancelable operating lease with an initial term ending after 123 months and an option to extend the lease for an additional five-year term. Under the lease agreement, we received a three-month free rent period, which commenced on August 15, 2018, and a tenant improvement allowance up to $3.8 million. We provided the lessor with a letter of credit to secure its obligations under the lease in the initial amount of $2.4 million, to be reduced to $1.8 million on the third anniversary of the rent commencement date and to $1.2 million on the fifth anniversary of the rent commencement date if we meet certain conditions set forth in the lease at each such time.

When we determined our lease term for our operating lease right-of-use assets and lease liabilities for these leases, we did not include the extension options for these leases in the original lease term.

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

	At December 31, 2020
Right-of-use operating lease assets (1)	$ 13.1
Operating lease liabilities (2)	$ 17.3
Weighted average remaining lease term	7.2 years
Weighted average discount rate	7.0%

(1) Included in deposits and other assets on our consolidated balance sheet.

(2) Current portion of $2.0 million was included in current portion of long-term obligations on our consolidated balance sheet, with the difference included in long-term obligations.

During the years ended December 31, 2020, 2019, and 2018 we paid $3.8 million, $3.9 million and $1.7 million of lease payments, which were included in operating activities in our consolidated statement of cash flows.

As of December 31, 2020, the future payments for our operating lease liabilities are as follows (in thousands):

	Operating Leases
Year ending December 31,	$
2021	3,193
2022	2,968
2023	2,707
2024	2,583
2025	2,442
Thereafter	7,038
Total minimum lease payments	20,931
Less:	
Imputed interest	(3,621)
Total operating lease liabilities	$ 17,310

Rent expense was $3.7 million, $3.6 million and $2.6 million for the years ended December 31, 2020, 2019 and 2018, respectively.

4. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15 million shares of "blank check" Preferred Stock. As of December 31, 2020, there were no shares of Preferred Stock outstanding. We have designated Series C Junior Participating Preferred Stock but have no issued or outstanding shares as of December 31, 2020.

Common Stock

At December 31, 2020 and 2019, we had 300 million shares of common stock authorized, of which 140.4 million and 140.3 million were issued and outstanding, respectively. As of December 31, 2020, total common shares reserved for future issuance were 26.1 million.

During the years ended December 31, 2020, 2019 and 2018, we issued 1.7 million, 3.1 million and 1.5 million shares of common stock, respectively, for stock option exercises, vesting of restricted stock units, and ESPP purchases. We received net proceeds from these transactions of $52.0 million, $119.7 million and $27.9 million in 2020, 2019 and 2018, respectively.

Share Repurchase Program

In September 2019, our board of directors approved a share repurchase program of up to $125 million of our common stock. In 2019, we repurchased 535,000 shares for $34.4 million. In the first quarter of 2020, we repurchased an additional 1.5 million shares for $90.5 million.

Stock Plans

1989 Stock Option Plan

In June 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20.0 million shares of common stock to our employees, directors, and consultants. The plan expires in January 2024. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 25percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. At December 31, 2020, a total of 30 thousand options were outstanding, of which options to purchase 30 thousand shares were exercisable, and 50 thousand shares were available for future grant under the 1989 Plan.

2011 Equity Incentive Plan

In March 2011, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, and performance cash awards to our employees, directors, and consultants. In June 2015, May 2017 and June 2019, after receiving approval from our stockholders, we amended our 2011 Equity Incentive Plan to increase the total number of shares reserved for issuance. We increased the shares available under our 2011 Equity Incentive Plan from 5.5 million to 11.0 million in June 2015, from 11.0 million to 16.0 million in May 2017 and from 16.0 million to 23.0 million in June 2019. The plan expires in June 2031. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only options and restricted stock unit awards to our employees, directors and consultants. We have granted restricted stock unit awards to our employees under the 2011 Plan which vest annually over a four-year period. At December 31, 2020, a total of 11.4 million options were outstanding, of which 6.7 million were exercisable, 2.2 million restricted stock unit awards were outstanding, and 4.3 million shares were available for future grant under the 2011 Plan.

Under the 2011 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur. The stock options and restricted stock unit awards we issued to Dr. Stanley T. Crooke in his former role as chief executive officer and certain stock options and restricted stock unit awards we issued to B. Lynne Parshall in her former role as chief operating officer will accelerate upon a change of control, as defined in the 2011 Plan. In addition, we implemented a change of control and severance benefit plan that provides for change of control and severance benefits to our executive officers, including our chief executive officer and chief financial officer. If we terminate one of our executive officers or if an executive officer resigns for good reason during the period that begins three months before and ends twelve months following a change in control of the company, the impacted executive officers' stock options and RSUs vesting will accelerate for options and RSUs outstanding as of the termination date.

2020 Equity Incentive Plan

In connection with the Akcea Acquisition in October 2020, we assumed the unallocated portion of the available share reserve under the Akcea 2015 Equity Incentive Plan. In December 2020, we amended and restated the Akcea 2015 equity plan, including renaming the plan as the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, or 2020 Plan. The 2020 Plan provided for the issuance of up to 2.6 million shares of our Common Stock to our employees, directors and consultants who were employees of Akcea prior to the Akcea Acquisition.

The plan expires in December 2025. The 2020 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only options and restricted stock unit awards to our eligible employees, directors and consultants. We have granted stock options to our employees under the 2020 Plan which vest annually over a four-year period. At December 31, 2020, a total of 0.01 million options were outstanding, of which none were exercisable, and 2.6 million shares were available for future grant under the 2020 Plan.

Under the 2020 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur.

Corporate Transactions and Change in Control under 2011 and 2020 Plans

In the event of certain significant corporate transactions, our Board of Directors has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 and 2020 Plans:

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and
- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options and restricted stock units to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan, or the 2002 Plan. In June 2015, after receiving approval from our stockholders, we amended our 2002 Plan to increase the total number of shares reserved for issuance from 1.2 million to 2.0 million. In June 2020, after receiving approval from our stockholders, we further amended our 2002 Plan. The amendments included:

- An increase to the total number of shares reserved for issuance under the plan from 2.0 million to 2.8 million shares;
- A reduction to the amount of the automatic awards under the plan;
- A revision to the vesting schedule of new awards granted; and
- An extension of the term of the plan.

Options under this plan expire 10 years from the date of grant. At December 31, 2020, a total of 1.0 million options were outstanding, of which 0.6 million were exercisable, 0.1 million restricted stock unit awards were outstanding, and 0.8 million shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In June 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years until 2019, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 3.2 million shares authorized under the plan as of December 31, 2020. The ESPP permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10percent of each employee's compensation) at the lower of 85percent of fair market value at the beginning of the purchase period or the end of each purchase period. Under the amended and restated ESPP, employees must hold the stock they purchase for a minimum of six months from the date of purchase. During 2020, employees purchased and we issued to employees 0.06 million shares under the ESPP at a weighted average price of $43.65 per share. At December 31, 2020, there were 0.7 million shares available for purchase under the ESPP.

Stock Option Activity

The following table summarizes the stock option activity under our stock plans for the year ended December 31, 2020 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Exercise Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2019	11,001	$ 51.48		
Granted	2,764	$ 59.89		
Exercised	(1,069)	$ 40.88		
Cancelled/forfeited/expired	(361)	$ 56.48		
Outstanding at December 31, 2020	12,335	$ 54.14	4.16	$ 55,885
Exercisable at December 31, 2020	7,366	$ 52.45	3.16	$ 43,267

The weighted-average estimated fair values of options granted were $29.43, $28.76 and $25.49 for the years ended December 31, 2020, 2019 and 2018, respectively. The total intrinsic value of options exercised during the years ended December 31, 2020, 2019 and 2018 were $15.5 million, $83.8 million and $34.8 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $43.7 million, $105.9 million and $18.9 million for the years ended December 31, 2020, 2019 and 2018, respectively. For the year ended December 31, 2020, the weighted-average fair value of options exercised was $55.33. As of December 31, 2020, total unrecognized compensation cost related to non-vested stock options was $54.1 million. We expect to recognize this cost over a weighted average period of 1.1 years. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures.

Restricted Stock Unit Activity

The following table summarizes the RSU activity for the year ended December 31, 2020 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2019	1,866	$ 55.80
Granted	1,244	$ 60.86
Vested	(602)	$ 53.68
Cancelled/forfeited	(134)	$ 58.96
Non-vested at December 31, 2020	2,374	$ 58.81

For the years ended December 31, 2020, 2019 and 2018, the weighted-average grant date fair value of RSUs granted was $60.86, $60.23 and $51.06 per RSU, respectively. As of December 31, 2020, total unrecognized compensation cost related to RSUs was $55.3 million. We expect to recognize this cost over a weighted average period of 1.3 years. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures.

Stock-based Compensation Expense and Valuation Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2020, 2019 and 2018 (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Cost of products sold	$ 1,991	$ 438	$ 160
Research, development and patent	115,584	95,348	76,557
Selling, general and administrative	112,542	50,788	54,595
Total	$ 230,117	$ 146,574	$ 131,312

Our non-cash stock-based compensation expense included $94.8 million, $37.1 million and $44.3 million of stock-based compensation expense for Akcea employees for the years ended December 31, 2020, 2019 and 2018, respectively.

In October 2020, as part of the Akcea Acquisition, Akcea's outstanding equity awards vested under Akcea's Plan. As a result, in the fourth quarter of 2020, we recognized all unrecognized stock-based compensation ($59.3 million) under Akcea's Plan. See Note 7, *Akcea Acquisition*, in the Notes to the Consolidated Financial Statements for further details.

In the third quarter of 2019, three Akcea executive officers terminated their employment and entered into separation agreements with Akcea. As a result, in the third quarter of 2019, Akcea reversed $19.1 million of stock-based compensation expense it had previously recognized related to the executive officers' stock options and RSUs that were no longer going to vest.

Determining Fair Value

Valuation. We measure stock-based compensation expense for equity-classified awards, principally related to stock options, RSUs, and stock purchase rights under the ESPP at the grant date, based on the estimated fair value of the award and we recognize the expense over the employee's requisite service period. We value RSUs based on the market price of our common stock on the date of grant.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on actual and projected exercise patterns. We recognize compensation expense for stock options granted, RSUs, and stock purchase rights under the ESPP using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), we recognize compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

For the years ended December 31, 2020, 2019 and 2018, we used the following weighted-average assumptions in our Black-Scholes calculations:

Ionis Employee Stock Options:

	December 31,		
	2020	**2019**	**2018**
Risk-free interest rate	1.5%	2.3%	2.4%
Dividend yield	0.0%	0.0%	0.0%
Volatility	58.6%	60.3%	63.0%
Expected life	4.7 years	4.8 years	4.6 years

Ionis Board of Director Stock Options:

	December 31,		
	2020	**2019**	**2018**
Risk-free interest rate	0.5%	1.9%	2.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	57.6%	60.7%	61.5%
Expected life	6.7 years	6.6 years	6.6 years

Ionis ESPP:

	December 31,		
	2020	**2019**	**2018**
Risk-free interest rate	0.8%	2.4%	1.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	47.9%	45.6%	47.3%
Expected life	6 months	6 months	6 months

Risk-Free Interest Rate. We base the risk-free interest rate assumption on observed interest rates appropriate for the term of our stock option plans or ESPP.

Dividend Yield. We base the dividend yield assumption on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future.

Volatility. We use an average of the historical stock price volatility of our stock for the Black-Scholes model. We computed the historical stock volatility based on the expected term of the awards.

Expected Life. The expected term of stock options we have granted represents the period of time that we expect them to be outstanding. We estimated the expected term of options we have granted based on actual and projected exercise patterns.

Forfeitures. We reduce stock-based compensation expense for estimated forfeitures. We estimate forfeitures at the time of grant and revise, if necessary, in subsequent periods if actual forfeitures differ from those estimates. We estimate forfeitures based on historical experience.

In addition to our stock plans, Akcea had its own stock plan prior to the Akcea Acquisition, referred to as the Akcea 2015 Equity Incentive Plan, or Akcea Plan. Under the Akcea Plan, Akcea granted options and RSUs.

For the years ended December 31, 2020, 2019 and 2018, we used the following weighted-average assumptions in our Black-Scholes calculations for the Akcea Plan:

Akcea Employee Stock Options:

	December 31,		
	2020	**2019**	**2018**
Risk-free interest rate	1.1%	2.2%	2.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	75.0%	75.4%	77.1%
Expected life	6.08 years	6.09 years	6.08 years

Akcea Board of Director Stock Options:

	December 31,		
	2020	**2019**	**2018**
Risk-free interest rate	0.8%	1.8%	2.9%
Dividend yield	0.0%	0.0%	0.0%
Volatility	75.3%	73.8%	78.2%
Expected life	5.67 years	6.25 years	6.42 years

Akcea ESPP:

	December 31,		
	2020	**2019**	**2018**
Risk-free interest rate	1.0%	2.4%	1.9%
Dividend yield	0.0%	0.0%	0.0%
Volatility	71.9%	60.0%	64.2%
Expected life	6 months	6 months	6 months

The following summarizes the Black-Scholes input methodology for Akcea options that differs from the methodology we use for Ionis options:

Volatility. Since Akcea did not have sufficient history to estimate the volatility of its common stock, Akcea calculated its expected volatility based on a blend of its historical volatility and reported data from selected publicly traded peer companies for which historical information was available.

Expected Life. Since Akcea did not have sufficient historical information, it used the simplified method for estimating its expected term. Under the simplified method Akcea calculated its expected term as the average time-to-vesting and the contractual life of the options.

Akcea RSU's

The fair value of RSUs was based on the market price of Akcea's common stock on the date of grant. Akcea granted RSUs with various vesting terms between six months and four years. The weighted-average grant date fair value of RSUs granted to employees for years ended December 31, 2020 and 2019 was $15.57 and $21.95 per share, respectively.

5. Income Taxes

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

	Year Ended December 31,		
	2020	**2019**	**2018**
United States	$ (172,702)	$ 344,280	$ (69,576)
Foreign	2,670	2,489	(6,580)
Income (loss) before income taxes	$ (170,032)	$ 346,769	$ (76,156)

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

	Year Ended December 31,		
	2020	**2019**	**2018**
Current:			
Federal	$ (837)	$ 35,861	$ 438
State	3,782	14,329	(1,442)
Foreign	518	413	374
Total current income tax expense (benefit)	3,463	50,603	(630)
Deferred:			
Federal	313,271	(7,096)	(290,511)
State	—	—	—
Total deferred income tax benefit	313,271	(7,096)	(290,511)
Total income tax expense (benefit)	$ 316,734	$ 43,507	$ (291,141)

Our expense (benefit) for income taxes differs from the amount computed by applying the U.S. federal statutory rate to income (loss) before taxes. The sources and tax effects of the differences are as follows (in thousands):

	Year Ended December 31,					
	2020		**2019**		**2018**	
Pre-tax income (loss)	$ (170,032)		$ 346,769		$ (76,156)	
Statutory rate	(35,707)	21.0%	72,822	21.0%	(15,993)	21.0%
State income tax net of federal benefit	(39,230)	23.1%	49,119	14.2%	(2,202)	2.9%
Foreign	49	0.0%	340	0.1%	1,735	(2.3)%
Net change in valuation allowance	437,597	(257.4)%	(37,765)	(10.9)%	(277,924)	364.9%
Net operating loss expiration	—	0.0%	—	0.0%	8,864	(11.6)%
TEGSEDI licensing gain	—	0.0%	—	0.0%	59,583	(78.2)%
Impact from outside basis differences	—	0.0%	(16,344)	(4.7)%	—	0.0%
Tax credits	(18,774)	11.0%	(22,296)	(6.4)%	(73,362)	96.3%
Deferred tax true-up	(206)	0.1%	646	0.2%	9,947	(13.1)%
Tax rate change	(29,131)	17.1%	1,811	0.5%	(1,808)	2.4%
Non-deductible compensation	7,931	(4.7)%	3,361	1.0%	3,154	(4.1)%
Other non-deductible items	193	(0.1)%	329	0.1%	(569)	0.7%
Stock-based compensation	17,435	(10.3)%	(4,837)	(1.4)%	(4,199)	5.5%
Foreign-derived intangible income benefit	—	0.0%	(2,071)	(0.6)%	—	0.0%
Impacts from Akcea Acquisition	(22,032)	13.0%	—	—	—	—
Other	(1,391)	0.8%	(1,608)	(0.5)%	1,633	(2.1)%
Effective rate	$ 316,734	(186.4)%	$ 43,507	12.6%	$ (291,141)	382.3%

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes.

Significant components of our deferred tax assets and liabilities as of December 31, 2020 and 2019 are as follows (in thousands):

	Year Ended December 31,	
	2020	2019
Deferred Tax Assets:		
Net operating loss carryovers	$ 83,681	$ 20,191
Tax credits	245,746	210,455
Deferred revenue	124,452	127,763
Stock-based compensation	80,055	65,703
Intangible and capital assets	98,443	77,861
Other	13,402	12,510
Total deferred tax assets	$ 645,779	$ 514,483
Deferred Tax Liabilities:		
Convertible debt	$ (2,920)	$ (6,110)
Fixed assets	(3,611)	(1,958)
Other	(5,808)	(3,884)
Net deferred tax asset	$ 633,440	$ 502,531
Valuation allowance	(633,440)	(196,974)
Total net deferred tax assets and liabilities	$ —	$ 305,557

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

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

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

Our valuation allowance increased by $436 million from December 31, 2019 to December 31, 2020. $313 million of the increase related to the valuation allowance established against our beginning of the year balance of Ionis' U.S. federal net deferred tax assets as discussed above, which resulted in us recognizing income tax expense during 2020. The remaining increase in our valuation allowance related to current year changes in our net deferred tax assets.

At December 31, 2020, we had federal and state, primarily California, tax net operating loss carryforwards of $243.3 million and $346.3 million, respectively. Our federal tax loss carryforwards are available indefinitely. Our California tax loss carryforwards will begin to expire in 2031. At December 31, 2020, we also had federal and California research and development tax credit carryforwards of $210.5 million and $87.4 million, respectively. Our Federal research and development tax credit carryforwards will begin to expire in 2034. Our California research and development tax credit carryforwards are available indefinitely.

Utilization of the net operating loss and tax credit carryforwards may be subject to an annual limitation due to the ownership change limitations provided by the Internal Revenue Code of 1986, as amended, and similar state provisions. The annual limitation may result in the expiration of net operating losses and credits before utilization.

We analyze filing positions in all U.S. federal, state and foreign jurisdictions where we file income tax returns, and all open tax years in these jurisdictions to determine if we have any uncertain tax positions on any of our income tax returns. We recognize the impact of an uncertain tax position on an income tax return at the largest amount that the relevant taxing authority is more-likely-than not to sustain upon audit. We do not recognize uncertain income tax positions if they have less than 50 percent likelihood of the applicable tax authority sustaining our position.

The following table summarizes our gross unrecognized tax benefits (in thousands):

	Year Ended December 31,		
	2020	2019	2018
Beginning balance of unrecognized tax benefits	$ 69,784	$ 68,301	$ 78,014
Decrease for prior period tax positions	(24,154)	(867)	(12,814)
Increase for prior period tax positions	7,023	736	—
Increase for current period tax positions	1,510	1,614	3,101
Ending balance of unrecognized tax benefits	$ 54,163	$ 69,784	$ 68,301

Included in the balance of unrecognized tax benefits at December 31, 2020 and 2019 was $6.4 million and $0.4 million respectively, that if we recognized, could impact our effective tax rate, subject to our remaining valuation allowance. None of our unrecognized tax benefits recorded at December 31, 2018 would impact our effective tax rate, if we recognized them.

We do not foresee any material changes to our gross unrecognized tax benefits within the next twelve months.

We recognize interest and/or penalties related to income tax matters in income tax expense. During the year ended December 31, 2020, we recognized $0.3 million of accrued interest and penalties related to gross unrecognized tax benefits. We did not record any accrued interest and penalties for the years ended December 31, 2019 and 2018.

We are subject to taxation in the U.S. and various state and foreign jurisdictions. Our tax years for 1999 through 2019 are subject to examination by the U.S. federal, state and foreign tax authorities.

We do not provide for a U.S. income tax liability and foreign withholding taxes on undistributed foreign earnings of our foreign subsidiaries as we consider those earnings to be permanently reinvested. It is not practicable for us to calculate the amount of unrecognized deferred tax liabilities associated with these earnings.

6. Collaborative Arrangements and Licensing Agreements

Strategic Partnership

Biogen

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

Spinal Muscular Atrophy Collaborations

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. SPINRAZA is approved in over 50 countries around the world. From inception through December 2020, we earned more than $1.3 billion in total revenue under our SPINRAZA collaboration, including more than $930 million in revenue from SPINRAZA royalties and more than $435 million in R&D revenue. We are receiving tiered royalties ranging from 11 percent to 15 percent on net sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on net sales of SPINRAZA. Biogen is responsible for all global development, regulatory and commercialization activities and costs for SPINRAZA. We completed our performance obligations under our collaboration in 2016.

New antisense medicines for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen has the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for global development, regulatory and commercialization activities and costs for such therapies. Under the collaboration agreement, we received a $25 million upfront payment in the fourth quarter of 2017. We will receive development and regulatory milestone payments from Biogen if new medicines advance towards marketing approval. In total over the term of our collaboration, we are eligible to receive up to $1.2 billion in license fees, milestone payments and other payments, including up to $80 million for the achievement of development milestones, up to $180 million for the achievement of commercialization milestones and up to $800 million for the achievement of sales milestones. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales. We will achieve the next payment of up to $60 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 recognized revenue as we performed services based on our effort to satisfy our performance obligation relative to the total effort expected to satisfy our performance obligation. We completed our performance obligation earlier than we previously estimated, as a result, we recognized $8.3 million of additional revenue in the fourth quarter of 2019. We do not have any remaining performance obligations under this collaboration. We will receive development and regulatory milestone payments from Biogen if Biogen advances the development candidate under this collaboration toward marketing approval.

Neurology Collaborations

2018 Strategic Neurology

In April 2018, we and Biogen entered into a strategic collaboration to develop novel antisense medicines for a broad range of neurological diseases and entered into a SPA. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for these diseases for 10 years. We are responsible for the identification of antisense drug candidates based on selected medicines. Biogen is responsible for conducting IND-enabling toxicology studies for the selected medicine. Biogen will have the option to license the selected medicine after it completes the IND-enabling toxicology study. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine.

In the second quarter of 2018, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at an approximately 25 percent cash premium and $375 million in an upfront payment. We are eligible to receive up to $270 million in milestone payments for each medicine that achieves marketing approval. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales. We are advancing eight programs under this collaboration and from inception through December 2020, we have received $1.05 billion in payments under this collaboration. We will achieve the next payment of $7.5 million if we advance a programunder this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined our transaction price to be $552 million, comprised of $375 million from the upfront payment and $177 million for the premium paid by Biogen for its purchase of our common stock. We determined the fair value of the premium we received by using the stated premium in the SPA and applying a lack of marketability discount. We included a lack of marketability discount in our valuation of the premium because Biogen received restricted shares of our common stock. We allocated the transaction price to our single performance obligation.

From inception through December 2020, we have included $608 million in payments in the transaction price for our R&D services performance obligation under this collaboration, including $11 million of milestone payments we achieved in 2020 and $30 million of milestone payments we achieved in 2019. These milestone payments did not create new performance obligations because they are part of our original R&D services performance obligation. Therefore, we included these amounts in our transaction price for our R&D services performance obligation in the period we achieved the milestone payment. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation at the end of the contractual term in June 2028.

2013 Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license medicines resulting from this collaboration. We will usually be responsible for drug discovery and early development of antisense medicines and Biogen will have the option to license antisense medicines after Phase 2 proof-of-concept. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. We are currently advancing six investigational medicines in development under this collaboration, including a medicine for Parkinson's disease (ION859), three medicines for ALS (tofersen, IONIS-C9$_{Rx}$ and ION541), a medicine for multiple system atrophy (ION464) and a medicine for an undisclosed target. In the fourth quarter of 2018, Biogen exercised its option to license our most advanced ALS medicine, tofersen, our medicine in Phase 3 development for SOD1 ALS. As a result, Biogen is now responsible for global development, regulatory and commercialization activities and costs for tofersen.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all medicines developed under this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and milestone payments per program. The $260 million per program consists of approximately $60 million in development milestones, including amounts related to the cost of clinical trials, and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any antisense medicines developed under this collaboration. From inception through December 2020, we have received over $270 million in upfront fees, milestone payments and other payments under this collaboration. We will achieve the next payment of up to $10 million if we advance a program under this collaboration.

At the commencement of our 2013 strategic neurology collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. At inception, we determined the transaction price to be the $100 million upfront payment we received and allocated it to our single performance obligation. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. In the third quarter of 2019, we updated our estimate of the total effort we expect to expend to satisfy our performance obligation. As a result, we recorded a cumulative catch up adjustment of $16.5 million to decrease revenue in the third quarter of 2019. During 2020, we completed our remaining research and development services and recognized the remaining revenue related to this performance obligation. From inception through the completion of our R&D services performance obligation in 2020, we included $145 million in total payments in the transaction price for our R&D services performance obligation.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter we generated the payment because we did not have any performance obligations for the respective payment. The following are the payments we earned:

- In the third quarter of 2018, we earned a $10 million milestone payment when Biogen initiated a Phase 1 study of IONIS-C9$_{Rx}$.
- In the fourth quarter of 2018, we earned a $35 million license fee when Biogen licensed tofersen from us because Biogen had full use of the licenses without any continuing involvement from us.
- In the fourth quarter of 2018, we earned a $5 million milestone when Biogen initiated a Proof-of-Concept study for tofersen.
- In the third quarter of 2019, we earned an $8 million milestone payment when Biogen initiated a Phase 1/2 study of ION859 for the treatment of people with Parkinson's disease under this collaboration.
- In the fourth quarter of 2019, we earned a $10 million milestone payment when Biogen advanced IONIS-C9$_{Rx}$.
- In the third quarter of 2020, we earned $18 million in milestone payments when Biogen initiated a Phase 1/2 trial for ION464, an investigational medicine in development targeting alpha-synuclein to treat patients with multiple system atrophy.
- In the third quarter of 2020, we earned a $10 million milestone payment when Biogen initiated a Phase 1/2 trial for ION541, an investigational medicine in development targeting ataxin 2 to treat patients with ALS.

2012 Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense medicines to treat neurodegenerative diseases. We are responsible for the development of each of the medicines through the completion of the initial Phase 2 clinical study for such medicine. Biogen has the option to license a medicine from each of the programs through the completion of the first Phase 2 study for each program. Under this collaboration, we are currently advancing IONIS-MAPT$_{Rx}$ for Alzheimer's disease and ION582 for Angelman syndrome. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. In the fourth quarter of 2019, Biogen exercised its option to license IONIS-MAPT$_{Rx}$. We are responsible for completing the Phase 1/2 in study patients with mild AD and a one-year long-term extension study. Biogen will have responsibility for global development, regulatory and commercialization activities and costs for IONIS-MAPT$_{Rx}$.

Under the terms of the agreement, we received an upfront payment of $30 million. Over the term of the collaboration, we are eligible to receive up to $210 million in a license fee and milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. The $210 million per program consists of up to $10 million in development milestone payments, plus a mark-up on the cost estimate of the Phase 1 and 2 studies and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales of any medicines resulting from each of the three programs. From inception through December 2020, we have received $154 million in payments under this collaboration, including $19.5 million we received from Biogen for achieving milestones for advancing IONIS-MAPT$_{Rx}$ during 2020. We will achieve the next payment of $25 million if we continue to advance IONIS-MAPT$_{Rx}$.

Under our collaboration, we determined we had a performance obligation to perform R&D services. We allocated $40 million in total payments to the transaction price for our R&D services performance obligation. In the third quarter of 2019, we completed our R&D services performance obligation when we designated a development candidate and Biogen accepted the development candidate. Biogen's decision to accept the development candidate was not within our control. We were recognizing revenue as we performed services based on our effort to satisfy our performance obligation relative to the total effort expected to satisfy our performance obligation. Because Biogen accepted the development candidate earlier than when we were previously estimating, we recognized $6.3 million of accelerated revenue in the third quarter of 2019.

When we commenced development for IONIS-MAPT$_{Rx}$ we identified our development work as a separate performance obligation. We are recognizing our IONIS-MAPT$_{Rx}$ development performance obligation based on the percentage of completion. From inception through December 2020, we have included $57 million in the transaction price for our IONIS-MAPT$_{Rx}$ development performance obligation. We currently estimate we will satisfy our performance obligation in 2022. Our total transaction price for our IONIS-MAPT$_{Rx}$ development performance obligation includes the following payments we achieved in 2019 and 2020 related to our development work:

- In the second quarter of 2019, we achieved a $7.5 million milestone payment from Biogen when we advanced IONIS-MAPT$_{Rx}$.
- In the fourth quarter of 2019, we achieved a $12 million milestone payment from Biogen when we entered into an agreement to conduct a long-term extension study for IONIS-MAPT$_{Rx}$.
- In the first quarter of 2020, we achieved a $7.5 million milestone payment from Biogen when we advanced IONIS-MAPT$_{Rx}$.
- In the third quarter of 2020, we achieved a $12 million milestone payment from Biogen when we advanced IONIS-MAPT$_{Rx}$ in the long-term extension study for IONIS-MAPT$_{Rx}$.

In the fourth quarter of 2019, we identified another performance obligation upon Biogen's license of IONIS-MAPT$_{Rx}$ because the license we granted to Biogen is distinct from our other performance obligations. We recognized the $45 million license fee for IONIS-MAPT$_{Rx}$ as revenue at that time because Biogen had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Biogen.

In the fourth quarter of 2019, we earned a $10 million milestone payment when Biogen advanced ION582. We recognized this milestone payment in full in the fourth quarter of 2019 because we did not have any performance obligations related to this milestone payment.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Year Ended December 31,		
	2020	**2019**	**2018**
SPINRAZA royalties (commercial revenue)	$ 286.6	$ 293.0	$ 237.9
R&D revenue	122.0	180.6	137.1
Total revenue from our relationship with Biogen	$ 408.6	$ 473.6	$ 375.0
Percentage of total revenue	56%	42%	63%

Our consolidated balance sheet at December 31, 2020 and 2019 included deferred revenue of $465.8 million and $525.8 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

AstraZeneca

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

Cardiovascular, Renal and Metabolic Diseases Collaboration

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

- ION449 (formerly IONIS-AZ4-2.5-L$_{Rx}$), an investigational medicine we designed to reduce the liver production of PCSK9 and lower the plasma level of LDL-C and thus reduce the risk of cardiovascular disease;
- ION532, an investigational medicine we designed to reduce the production of APOL1 for the treatment of APOL1-associated chronic kidney disease;
- ION839, an investigational medicine we designed to inhibit the production of PNPLA3 protein, a major genetic determinant of NASH progression; and
- ION455, an investigational medicine we designed as a potential treatment for NASH.

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

Under the terms of the agreement, we received a $65 million upfront payment. We are eligible to receive license fees and milestone payments of up to more than $5.5 billion as medicines under this collaboration advance, including up to $1.1 billion for the achievement of development milestones, up to $2.9 billion for regulatory milestones and up to $1.5 billion for commercial milestones. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. We will achieve the next payment of up to $30 million under this collaboration if AstraZeneca advances a medicine under this collaboration. From inception through December 2020, we have received over $235 million in upfront fees, license fees, milestone payments, and other payments under this collaboration, including $30 million we earned in 2020 when AstraZeneca licensed ION455 and $30 million in milestone payments we earned in 2020 when AstraZeneca advanced ION532 and ION449 in development.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for AstraZeneca. We determined the transaction price to be the $65 million upfront payment we received and we allocated it to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy this performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy this performance obligation in the third quarter of 2021. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. From inception through December 2020, we have included $90 million in payments in the transaction price for our R&D services performance obligation.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. The following are the payments we have earned:

- In the first quarter of 2018, we earned two $30 million license fees when AstraZeneca licensed ION532 and ION839 because AstraZeneca had full use of the licenses without any continuing involvement from us.
- In the third quarter of 2018, we earned a $10 million milestone payment when AstraZeneca initiated a Phase 1 study of ION449.
- In the fourth quarter of 2019, we earned a $10 million milestone payment when AstraZeneca initiated a Phase 1 study of ION839.
- In the first quarter of 2020, we earned a $10 million milestone payment when AstraZeneca advanced ION532.
- In the fourth quarter of 2020, we earned a $20 million milestone payment when AstraZeneca advanced ION449.
- In the fourth quarter of 2020, we earned a $30 million license fee when AstraZeneca licensed ION455 because AstraZeneca had full use of the license without any continuing involvement from us.

Oncology Collaboration

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

Under the terms of this agreement, we received $31 million in upfront payments. We are eligible to receive milestone payments and license fees up to more than $265 million under this collaboration, including up to $107 million for the achievement of development milestones and up to $105 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. From inception through December 2020, we have received over $140 million in upfront fees, milestone payments, and other payments under this oncology collaboration, including $13 million we earned when AstraZeneca licensed ION736 in 2020. We will achieve the next payment of $12 million if AstraZeneca advances ION736 in development.

We completed all of the performance obligations we identified under this collaboration in the first quarter of 2018.

Under this collaboration, we have also generated additional payments that we concluded were not part of other performance obligations discussed above. We recognized each of these payments in full in the respective quarter we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. The following are the payments we have earned:

- In the fourth quarter of 2018, we earned a $17.5 million milestone payment and a $10 million milestone payment when AstraZeneca advanced two programs under our collaboration.
- In the second quarter of 2020, we earned a $13 million license fee when AstraZeneca licensed ION736 because AstraZeneca had full use of the license without any continuing involvement from us.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with AstraZeneca (in millions, except percentage amounts):

	Year Ended December 31,		
	2020	2019	2018
R&D revenue	$ 88.0	$ 28.1	$ 120.7
Percentage of total revenue	12%	3%	20%

Our consolidated balance sheet at December 31, 2020 and 2019 included deferred revenue of $10.0 million and $25.0 million, respectively, related to our relationship with AstraZeneca.

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. We were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis. Under the terms of the agreement, we received a $100 million upfront payment in the second quarter of 2015. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. In conjunction with the decision to advance these programs, we received a $75 million payment from Bayer. In October 2019, Bayer decided it would advance IONIS-FXI-L$_{Rx}$ following positive clinical results. Bayer is now responsible for all global development, regulatory and commercialization activities and costs for the FXI program.

We are eligible to receive up to $385 million in license fees, milestone payments and other payments, including up to $125 million for the achievement of development milestones and up to $110 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of both medicines combined. From inception through December 2020, we have received over $185 million from this collaboration. We will achieve the next payment of $20 million if Bayer initiates a Phase 3 study for the FXI program.

At the commencement of this collaboration, we identified three performance obligations, the license of IONIS-FXI$_{Rx}$, R&D services and delivery of API, all of which we completed in 2016.

In February 2017, when we amended our collaboration with Bayer, we identified two new performance obligations, one for the license of IONIS-FXI-L$_{Rx}$ and one for R&D services. We determined the transaction price to be the $75 million payment. We allocated $64.9 million to the license of IONIS-FXI-L$_{Rx}$ based on its estimated relative stand-alone selling price and recognized the associated revenue upon our delivery of the license in the first quarter of 2017. We allocated $10.1 million to our R&D services performance obligation based on an estimated relative stand-alone selling price. We recognized revenue for our R&D services performance obligation as we performed services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We completed our obligation in the third quarter of 2019.

In the fourth quarter of 2019, we earned a $10 million milestone payment when Bayer decided it would advance IONIS-FXI-L$_{Rx}$. We recognized this milestone payment in full in the fourth quarter of 2019 because we did not have any performance obligations related to this milestone payment.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with Bayer (in millions, except percentage amounts):

	Year Ended December 31,		
	2020	2019	2018
R&D revenue	$ 3.2	$ 14.3	$ 5.0
Percentage of total revenue	0%	1%	1%

Our consolidated balance sheet at December 31, 2020 did not include any deferred revenue related to our relationship with Bayer. Our consolidated balance sheet at December 31, 2019 included deferred revenue of $2.4 million related to our relationship with Bayer.

GSK

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

Under our agreement, if GSK successfully develops these medicines and achieves pre-agreed sales targets, we could receive license fees and milestone payments of up to $262 million, including up to $47.5 million for the achievement of development milestones, up to $120 million for the achievement of regulatory milestones and up to $70 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that GSK successfully commercializes under this alliance. From inception through December 2020, we have received more than $190 million in payments under this alliance with GSK. We will achieve the next payment of $15 million if GSK initiates a Phase 3 study of a medicine under this program.

We completed our R&D services performance obligations under our collaboration in the first quarter of 2015. We identified a new performance obligation when we granted GSK the license of the HBV program and assigned related intellectual property rights in the third quarter of 2019 because the license was distinct from our other performance obligations. We recognized the $25 million license fee for the HBV program as revenue at that time because GSK had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to GSK.

We do not have any remaining performance obligations under our collaboration with GSK; however, we can still earn additional payments and royalties as GSK advances the HBV program.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with GSK (in millions, except percentage amounts):

	Year Ended December 31,		
	2020	**2019**	**2018**
R&D revenue	$ 0.2	$ 25.4	$ 1.6
Percentage of total revenue	0%	2%	0%

We did not have any deferred revenue from our relationship with GSK at December 31, 2020 and 2019.

Janssen Biotech, Inc.

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

Under the terms of the agreement, we received $35 million in upfront payments. We are eligible to receive up to more than $285 million in license fees and milestone payments for these programs, including up to $65 million for the achievement of development milestones, up to $160 million for the achievement of regulatory milestones and up to $60 million for the achievement of commercialization milestones. From inception through December 2020, we have received over $80 million from this collaboration. In addition, we are eligible to receive tiered royalties up to the near teens on net sales from any medicines resulting from this collaboration. We will achieve the next payment of $5 million if Janssen continues to advance ION253 in development.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Janssen. We determined the transaction price to be the $35 million upfront payments we received. We allocated the $35 million to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, which ended in the fourth quarter of 2017.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter in which we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. In the third quarter of 2020, we earned a $5 million milestone payment when Janssen initiated a Phase 1 trial for ION253.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with Janssen (in millions, except percentage amounts):

	Year Ended December 31,		
	2020	**2019**	**2018**
R&D revenue	$ 5.0	$ 0.1	$ 6.6
Percentage of total revenue	1%	0%	1%

We did not have any deferred revenue from our relationship with Janssen at December 31, 2020 and 2019.

Novartis

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

Under the collaboration, we are eligible to receive up to $675 million in milestone payments, including $25 million for the achievement of a development milestone, up to $290 million for the achievement of regulatory milestones and up to $360 million for the achievement of commercialization milestones. From inception through December 2020, we have received $249 million in upfront payments, milestone payments, license fees and other payments from this collaboration. We are also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of pelacarsen. We will achieve the next payment of $25 million if Novartis advances pelacarsen.

In conjunction with this collaboration, we entered into a SPA with Novartis. As part of the SPA, Novartis purchased 1.6 million shares of our common stock for $100 million in the first quarter of 2017. As part of the SPA, Novartis was required to purchase $50 million of Akcea's common stock at Akcea's IPO price or our common stock at a premium if an IPO did not occur by April 2018. Under the SPA, in the second quarter of 2017, Novartis purchased $50 million of Akcea's common stock in a separate private placement concurrent with the completion of Akcea's IPO at a price per share equal to the IPO price.

At the commencement of this collaboration, we identified four separate performance obligations:

- R&D services for pelacarsen;
- R&D services for IONIS-APOCIII-L_{Rx};
- API for pelacarsen; and
- API for IONIS-APOCIII-L_{Rx}.

We determined that the R&D services for each medicine and the API for each medicine were distinct performance obligations.

We determined our transaction price to be $108.4 million, comprised of the following:

- $75 million from the upfront payment;
- $28.4 million for the premium paid by Novartis for its purchase of our common stock at a premium in the first quarter of 2017; and
- $5.0 million for the potential premium Novartis would have paid if they purchased our common stock in the future.

We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- $64.0 million for the R&D services for pelacarsen;
- $40.1 million for the R&D services for IONIS-APOCIII-L_{Rx};
- $1.5 million for the delivery of pelacarsen API; and
- $2.8 million for the delivery of IONIS-APOCIII-L_{Rx} API.

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

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

We recognized revenue related to the R&D services for pelacarsen and IONIS-APOCIII-L_{Rx} performance obligations as we performed services based on our effort to satisfy our performance obligations relative to our total effort expected to satisfy our performance obligations.

During the years ended December 31, 2020 and 2019, we earned the following revenue from our relationship with Novartis (in millions, except percentage amounts):

	Year Ended December 31,		
	2020	**2019**	**2018**
R&D revenue	$ 1.0	$ 187.4	$ 50.6
Percentage of total revenue	0%	17%	8%

We did not have any deferred revenue from our relationship with Novartis at December 31, 2020 and 2019.

Pfizer

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

Under the terms of the agreement, we received a $250 million upfront payment. We are also eligible to receive development, regulatory and sales milestone payments of up to $1.3 billion, including up to $205 million for the achievement of development milestones, up to $250 million for the achievement of regulatory milestones and up to $850 million for the achievement of commercialization milestones. From inception through December 2020, we have received over $330 million, including a $75 million milestone payment we earned in the fourth quarter of 2020 when Pfizer began the Phase 2b study of vupanorsen. We are also eligible to earn tiered royalties in the mid-teens to low 20 percent range on annual worldwide net sales. Prior to regulatory filing for marketing approval, we have the right, at our option to participate in certain commercialization activities with Pfizer in the U.S. and certain additional markets on pre-defined terms and based on meeting pre-defined criteria. We will achieve the next payment of $50 million if Pfizer advances vupanorsen.

At the commencement of the license agreement, we identified three separate performance obligations:

- License of vupanorsen;
- R&D services for vupanorsen; and
- API for vupanorsen.

We determined the transaction price to be $250 million, the upfront payment we received. We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- $245.6 million for the license of vupanorsen;
- $2.2 million for the R&D services for vupanorsen; and
- $2.2 million for the delivery of vupanorsen API.

We are recognizing revenue related to each of our performance obligations as follows:

- We recognized $245.6 million for the license of vupanorsen in the fourth quarter of 2019 because we determined the license we granted to Pfizer was distinct from our other performance obligations and Pfizer had full use of the license without any continuing involvement from us.
- We recognized revenue related to the R&D services for vupanorsen as we performed services based on our effort to satisfy our performance obligation relative to our total effort to satisfy our performance obligation. We completed our R&D services in mid-2020.
- We recognized the amount attributed to the API supply for vupanorsen when we delivered it to Pfizer in the fourth quarter of 2019.

In the fourth quarter of 2020, we earned a $75 million milestone payment when Pfizer began the Phase 2b study of vupanorsen. We recognized this milestone payment in full in the fourth quarter of 2020 because we did not have any performance obligations related to this milestone payment.

During the years ended December 31, 2020 and 2019, we earned the following revenue from our relationship with Pfizer (in millions, except percentage amounts):

	Year Ended December 31,	
	2020	**2019**
R&D revenue	$ 82.1	$ 248.7
Percentage of total revenue	11%	22%

We did not have any deferred revenue from our relationship with Pfizer at December 31, 2020. Our consolidated balance sheet at December 31, 2019 included deferred revenue of $1.3 million related to our relationship with Pfizer.

PTC Therapeutics

In August 2018, we entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. Under the license agreement, we are eligible to receive up to $26 million in payments. From inception through December 2020, we have received $22 million from PTC. We are eligible to receive royalties from PTC in the mid-20 percent range on net sales in Latin America for each medicine. PTC’s obligation to pay us royalties begins on the earlier of 12 months after the first commercial sale of a product in Brazil or the date that PTC recognizes revenue of at least $10 million in Latin America.

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

Under this collaboration, we have also generated milestone payments that we concluded were not part of the performance obligations discussed above. We recognized each of these milestone payments in full in the respective quarter in which we achieved the milestone payment because the payments were distinct and we did not have any performance obligations for the respective payment. The following are the payments we have earned:

- In the second quarter of 2019, we earned a $6 million payment when WAYLIVRA was approved by the EMA.
- In the fourth quarter of 2019, we earned $4 million when TEGSEDI was approved in Brazil.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with PTC (in millions, except percentage amounts):

	Year Ended December 31,		
	2020	2019	2018
Licensing and other royalty revenue (commercial revenue)	$ 1.6	$ 10.2	$ 12.0
Percentage of total revenue	0%	1%	2%

Our consolidated balance sheet at December 31, 2020 and 2019 did not include any deferred revenue related to our relationship with PTC.

Roche

Huntington's Disease

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for HD based on our antisense technology. Under the agreement, we discovered and developed tominersen, an investigational medicine targeting HTT protein in Phase 3 development. We developed tominersen through completion of our Phase 1/2 clinical study in people with early stage HD. In the fourth quarter of 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen. Roche is responsible for all global development, regulatory and commercialization activities and costs for tominersen.

Under the terms of the agreement, we received an upfront payment of $30 million in April 2013 and an additional $3 million payment in 2017. We are eligible to receive up to $365 million in a license fee and milestone payments including up to $70 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional medicine successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on any net sales of any product resulting from this alliance. From inception through December 2020, we have received $150 million in upfront fees, milestone payments and license fees under this collaboration. We will achieve the next payment of $15 million if Roche advances tominersen.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Roche. We determined the transaction price to be the $30 million upfront payment we received and allocated it to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, which ended in the third quarter of 2017.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter in which we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. The following are the payments we have earned:

- In the fourth quarter of 2017, we earned a $45 million license fee when Roche licensed tominersen because Roche had full use of the license without any continuing involvement from us.
- In the first quarter of 2019, we earned $35 million in milestone payments when Roche dosed the first patient in the Phase 3 study of tominersen in the first quarter of 2019.

We do not have any remaining performance obligations related to tominersen under this collaboration with Roche; however, we can still earn additional payments and royalties as Roche advances tominersen.

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

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

Under the terms of this agreement, we received a $75 million upfront payment in the fourth quarter of 2018. We are eligible to receive up to $684 million in development, regulatory and sales milestone payments and license fees. In addition, we are also eligible to receive tiered royalties from the high teens to 20 percent on net sales. We will achieve the next payment of $20 million if we advance the Phase 2 study in patients with dry AMD.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Roche. We determined the transaction price to be the $75 million upfront payment we received and allocated it to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. During the fourth quarter of 2020, we updated our estimate of the total effort we expected to expend to satisfy our performance obligation under this collaboration. In the fourth quarter of 2020, we recorded a cumulative catch up adjustment of $9.2 million to decrease revenue because we updated our total cost estimate to complete the Phase 2 study of IONIS-FB-L_{Rx} for the treatment of patients with GA. We currently estimate we will satisfy our performance obligation in the fourth quarter of 2023.

During the years ended December 31, 2020, 2019 and 2018, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	Year Ended December 31,		
	2020	**2019**	**2018**
R&D revenue	$ 5.9	$ 57.0	$ 8.3
Percentage of total revenue	1%	5%	1%

Our consolidated balance sheet at December 31, 2020 and 2019 included deferred revenue of $47.2 million and $52.3 million related to our relationship with Roche, respectively.

Other Agreement

Alnylam Pharmaceuticals, Inc.

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

In the fourth quarter 2020, we completed an arbitration process with Alnylam. The arbitration panel awarded us $41.2 million for payments owed to us by Alnylam related to Alnylam's agreement with Sanofi Genzyme. We recognized the $41.2 million payment from Alnylam as revenue in the fourth quarter of 2020 because we did not have any performance obligations for the respective payment.

	Year Ended December 31,		
	2020	2019	2018
R&D revenue	$ 47.9	$ 24.1	$ 2.0
Percentage of total revenue	7%	2%	—

Our consolidated balance sheet at December 31, 2020 and 2019 did not include any deferred revenue related to our relationship with Alnylam.

7. Akcea Acquisition

Purchase Price and Direct Transaction Costs Accounting for the Akcea Acquisition

In October 2020, we acquired the shares of Akcea's common stock we did not own, increasing our ownership from 76 percent to 100 percent. Under the purchase agreement, we purchased 24.8 million shares at $18.15 per share, resulting in a total purchase price of $450.6 million.

To reflect our 100 percent ownership, we accounted for the increase in our ownership by eliminating the noncontrolling interest adjustment in stockholders' equity in accordance with the Consolidation accounting guidance (ASC Topic 810). We recognized the difference between the purchase price and the adjustment to noncontrolling interest in stockholders' equity as additional-paid-in capital. Refer to our *Statement of Stockholders' Equity* for detailed amounts.

We accounted for the transaction costs related to the Akcea Acquisition as a direct charge to stockholders' equity. We incurred $40.6 million of direct transaction costs from the Akcea Acquisition, primarily comprised of banking and legal fees.

Equity Award Payouts related to the Akcea Acquisition

In October 2020, as part of the Akcea Acquisition, Ionis cancelled all of Akcea's equity awards. In exchange for the cancelled awards, if eligible under the terms of the Acquisition, we paid holder's a cash payment. We paid $18.15 for each outstanding RSU. For each outstanding option with an exercise price less than $18.15, we paid $18.15 less the exercise price. As a result, we paid out $53.4 million in the fourth quarter of 2020 related to Akcea's cancelled equity awards. We accounted for these payments as part of the transaction costs recorded to stockholders' equity in the fourth quarter of 2020. Because we did not replace the Akcea awards, we recognized all unrecognized non-cash stock-based compensation ($59.3 million) under Akcea's Plan in our statement of operations in the post-acquisition period in the fourth quarter of 2020.

Severance and Retention Costs related to the Akcea Acquisition

As a result of the Akcea Acquisition, we expect to incur severance expenses of up to $9.3 million and retention expenses of up to $19.2 million. During the fourth quarter of 2020, we recorded $15.3 million of severance and retention related costs in operating expenses. We will recognize the remaining severance and retention costs through October 2021.

The following table summarizes the costs by category related to the Akcea Acquisition (in millions):

	Three Months Ended December 31, 2020
R&D expenses	$ 3.9
SG&A expenses	11.4
Total	$ 15.3

The following table summarizes the severance and retention reserve included in accrued compensation for the period indicated related to Akcea Acquisition (in millions):

	Three Months Ended December 31, 2020
Severance & retention reserve beginning balance	$ —
Severance & retention expensed during period	15.3
Amounts paid during the period	(0.6)
Severance & retention reserve ending balance	$ 14.7

8. Severance and Retention Costs related to our Restructured European Operations

In the fourth quarter of 2020, we entered into a distribution agreement with Sobi to commercialize TEGSEDI and WAYLIVRA in Europe. Under the distribution agreement, Sobi took over all material distribution operations at the end of January 2021. We remain the marketing authorization holder for TEGSEDI and WAYLIVRA in Europe. We will continue to maintain limited European operations including regulatory, manufacturing, and the management of relationships with key opinion leaders. We will also continue to lead the TEGSEDI and WAYLIVRA global commercial strategy.

As a result of this change, we expect to incur up to $14.8 million of severance and retention expenses. During the fourth quarter of 2020, we recorded $12.5 million of severance and retention related costs in operating expenses related to this agreement. We will recognize the remaining expenses through October 2021, of which we will recognize the majority of the remaining expenses in the first quarter of 2021.

The following table summarizes the costs by category related to our restructured European operations (in millions):

	Three Months Ended December 31, 2020
R&D expenses	$ 4.2
SG&A expenses	8.3
Total	$ 12.5

The following table summarizes the severance and retention reserve included in accrued compensation for the periods indicated related to our restructured European operations (in millions):

	Three Months Ended December 31, 2020
Severance & retention reserve beginning balance	$ —
Severance & retention expensed during period	12.5
Amounts paid during the period	(0.1)
Severance & retention reserve ending balance	$ 12.4

9. Segment Information and Concentration of Business Risk

Through 2020, we had two reportable segments, our Ionis Core segment and Akcea Therapeutics. We have provided segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviewed to assess operating performance and to make operating decisions through 2020. Segment income (loss) from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment, we are exploiting our antisense technology to generate a broad pipeline of first-in-class and/or best-in-class medicines for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy.

Akcea was focused on developing and commercializing medicines to treat patients with serious and rare diseases. Akcea generated revenue from TEGSEDI and WAYLIVRA product sales and from its collaborations.

The following tables show our segment revenue and income (loss) from operations for 2020, 2019 and 2018 (in thousands), respectively.

2020	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 286,583	$ —	$ —	$ 286,583
Product sales, net	—	69,999	—	69,999
Licensing and other royalty revenue	11,334	—	(3,217)	8,117
Total commercial revenue	297,917	69,999	(3,217)	364,699
R&D revenue under collaborative agreements	325,024	82,321	(42,780)	364,565
Total segment revenue	$ 622,941	$ 152,320	$ (45,997)	$ 729,264
Total operating expenses	$ 563,647	$ 389,575	$ (51,876)	$ 901,346
Income (loss) from operations	$ 59,294	$ (237,255)	$ 5,879	$ (172,082)

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
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)

The following table shows our total assets by segment at December 31, 2020 and 2019 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
December 31, 2020	$ 2,792,222	$ 435,824	$ (838,291)	$ 2,389,755
December 31, 2019	$ 3,478,081	$ 599,250	$ (844,219)	$ 3,233,112

Contracts receivables at December 31, 2020 was comprised of approximately 99.5percent from two significant partners. Contracts receivables at December 31, 2019 was comprised of approximately 75 percent from one significant partner.

10. Employment Benefits

We have employee 401(k) salary deferral plans covering all employees. Employees could make contributions by withholding a percentage of their salary up to the IRS annual limits of $19,500 and $26,000 in 2020 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately $5.7 million, $6.4 million and $5.7 million in matching contributions for the years ended December 31, 2020, 2019 and 2018, respectively.

11. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If the potential loss from any legal proceeding is considered probable and the amount can be reasonably estimated, we accrue a liability for the estimated loss. Significant judgment is required to determine the probability of a loss and whether the amount of the loss is reasonably estimable. The outcome of any proceeding is not determinable in advance. As a result, the assessment of a potential liability and the amount of accruals recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding, and may revise our estimates.

On July 16, 2020, a purported stockholder of Akcea filed an action in the Delaware Court of Chancery captioned John Makris, et al. v. Stanley T. Crooke, et al., C.A. No. 2020-0587, or the "Delaware Action." The plaintiff in the Delaware Action asserts claims against (i) current and former members of Akcea's board of directors; and (ii) Ionis, or collectively, the "Defendants". The plaintiff asserts derivative claims on behalf of Akcea, which is a nominal defendant in the Delaware Action, as well as putatively direct claims on behalf of a purported class of Akcea's stockholders. The plaintiff in the Delaware action asserts that the Defendants breached their fiduciary duties in connection with the licensing transaction that we and Akcea entered into regarding TEGSEDI and IONIS-TTR-L_{Rx}. The plaintiff also asserts an unjust enrichment claim against Ionis. The plaintiff's claims are similar to those asserted in a prior action in the Delaware Court of Chancery captioned City of Cambridge Retirement System v. Crooke, et al., C.A. No. 2019-0905, which was dismissed with prejudice to the named plaintiff only on April 8, 2020. We believe that the claims asserted in the Delaware Action are without merit and anticipate filing a motion to dismiss the claims.

In light of the August 31, 2020 public announcement of the Akcea Acquisition, the parties to the Delaware Action entered into a stipulation whereby the Defendants need to respond to the complaint filed on July 16, 2020, and the plaintiff will file an amended complaint. The amended complaint has not yet been filed.

12. Fourth Quarter Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized fourth quarter data for 2020 and 2019 are as follows (in thousands, except per share data).

Three Months Ended December 31,	**2020**	**2019**
Revenue	$ 290,281	$ 493,680
Operating expenses	$ 312,945	$ 233,028
Income (loss) from operations	$ (22,664)	$ 260,652
Net income (loss)	$ (341,426)	$ 203,957
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (340,271)	$ 184,415
Basic net income (loss) per share (1) (2)	$ (2.44)	$ 1.31
Diluted net income (loss) per share (1) (3)	$ (2.44)	$ 1.28

(1) We compute net income (loss) per share independently for each quarter during the year.

(2) As discussed in Note 1, *Organization and Significant Accounting Policies*, we compute basic net income (loss) per share by dividing the total net income (loss) attributable to our common stockholders by our weighted-average number of common shares outstanding during the period. Our basic net income (loss) per share calculation for each of the fourth quarters in 2020 and 2019 considered our net income (loss) for Ionis on a stand-alone basis plus our share of Akcea's net loss for the period. To calculate the portion of Akcea's net loss attributable to our ownership, we multiplied Akcea's loss per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net income (loss) available to Ionis common stockholders for the calculation of net income (loss) per share is different than net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders in the consolidated statements of operations.

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

Three Months Ended December 31 , 2020	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Loss Per Share Calculation
Akcea's net loss in the pre-acquisition period attributable to our ownership	77,095	$ (0.05)	$ (3,603)
Akcea's net loss in the post-acquisition period attributable to our ownership			(85,987)
Akcea's total net loss attributable to our ownership			$ (89,590)
Ionis' stand-alone net loss			(250,682)
Net loss available to Ionis common stockholders			$ (340,272)
Weighted average shares outstanding			139,956
Basic net loss per share			$ (2.44)

Three Months Ended December 31 , 2019	Weighted Average Shares Owned in Akcea	Akcea's Net Income Per Share	Basic Net Income Per Share Calculation
Common shares	71,342	$ 0.87	$ 62,243
Akcea's net income attributable to our ownership			$ 62,243
Ionis' stand-alone net income			121,552
Net income available to Ionis common stockholders			$ 183,795
Weighted average shares outstanding			140,583
Basic net income per share			$ 1.31

(3) We had net income available to Ionis common stockholders for the fourth quarter of 2019. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period as follows (in thousands except per share amounts):

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

EXHIBIT 10.18

IONIS PHARMACEUTICALS, INC.
PERFORMANCE BASED RESTRICTED STOCK UNIT GRANT NOTICE
(2011 EQUITY INCENTIVE PLAN)

Ionis Pharmaceuticals, Inc. (the ***"Company"***), pursuant to its Amended and Restated 2011 Equity Incentive Plan (the ***"Plan"***), hereby awards to Participant a Performance Based Restricted Stock Unit (***"PRSU"***) Award for the number of stock units set forth below (the ***"Award"***). The Award is subject to all of the terms and conditions as set forth herein; and in the Plan and the Performance Based Restricted Stock Unit Agreement (the ***"Agreement"***), both of which are attached hereto and incorporated herein in their entirety. Capitalized terms not otherwise defined herein shall have the meanings set forth in the Plan or the Agreement. In the event of any conflict between the terms in the Award and the Plan, the terms of the Plan shall control.

Participant:	
Date of Grant:	
Target Number of Stock Units Subject to Award:	
Maximum Number of Stock Units Subject to Award:	
Consideration:	Participant's Services

Vesting Schedule: Subject to Section 4(b) of the Agreement, if Participant ceases to be a Service Provider for any or no reason before Participant vests in the PRSU, the PRSU and Participant's right to acquire any Shares hereunder will immediately terminate.

Up to one third (1/3) of the maximum number of PRSUs subject to the Agreement are eligible for vesting at the end of each Performance Period depending on the Company's relative Total Shareholder Return over the applicable Performance Periods, but subject to the Alternative Three Year Performance Period Vested Unit Calculation (each as more fully described in the PRSU Agreement).

You must accept this Award prior to the first vesting date. If you do not accept this Award by the first vest date, this Award will automatically expire.

Issuance Schedule: The shares of Common Stock to be issued in respect of the Award will be issued in accordance with Section 1 of the Agreement.

Special Tax Withholding Right: *If permitted by the Company*, you may direct the Company (i) to withhold, from shares otherwise issuable in respect of the Award, a portion of those shares with an aggregate fair market value (measured as of the delivery date) equal to the amount of the applicable withholding taxes, and (ii) to make a cash payment equal to such fair market value directly to the appropriate taxing authorities, as provided in Section 12 of the Agreement.

Additional Terms/Acknowledgements: The undersigned Participant acknowledges receipt of, and understands and agrees to, this Grant Notice, the Agreement and the Plan. Participant further acknowledges that as of the Date of Grant, this Grant Notice, the Agreement and the Plan set forth the entire understanding between Participant and the Company regarding the Award and supersede all prior oral and written agreements on that subject, with the exception of any employment or severance arrangement that would provide for vesting acceleration of the Award upon the terms and conditions set forth therein.

IONIS PHARMACEUTICALS, INC.

By: _____
Signature

Title: _____

Date: _____

PARTICIPANT:

_____
Signature

Date: _____

ATTACHMENTS: Performance Based Restricted Stock Unit Agreement

IONIS PHARMACEUTICALS, INC.
AMENDED & RESTATED 2011 EQUITY INCENTIVE PLAN

PERFORMANCE BASED RESTRICTED STOCK UNIT AGREEMENT

Pursuant to the Performance Based Restricted Stock Unit Grant Notice ("***Grant Notice***") and this Performance Based Restricted Stock Unit Agreement ("***Agreement***") and in consideration of your services, Ionis Pharmaceuticals, Inc. (the "***Company***") has awarded you a Performance Based Restricted Stock Unit Award (the "***Award***") under its Amended & Restated 2011 Equity Incentive Plan (the "***Plan***"). Your Award is granted to you effective as of the Date of Grant set forth in the Grant Notice for this Award. This Agreement will be deemed to be agreed to by the Company and you upon the earlier of (i) signing (or electronic acceptance) by you of the Grant Notice to which it is attached, and (ii) your receipt of shares of Common Stock under this Agreement. Capitalized terms not explicitly defined in this Agreement will have the same meanings given to them in the Plan or the Grant Notice, as applicable. In the event of any conflict between the terms in this Agreement and the Plan, the terms of the Plan will control. The details of your Award, in addition to those set forth in the Grant Notice and the Plan, are as follows.

1. GRANT AND VESTING OF THE AWARD.

(a) This Award represents the right to be issued on a future date the number of shares of the Company's Common Stock that is equal to the number of performance based restricted stock units ("***PRSUs***") as described below. This Award was granted in consideration of your services to the Company. Except as otherwise provided herein, you will not be required to make any payment to the Company (other than past and future services to the Company) with respect to your receipt of the Award, the vesting of the PRSUs or the delivery of the Common Stock to be issued in respect of the Award.

(b) One third (1/3) of the maximum number of PRSUs subject to this Agreement are eligible for vesting at the end of each Performance Period depending on the Company's relative Total Shareholder Return over the applicable Performance Period, but *subject to* the Alternative Three Year Performance Period Vested Unit Calculation (each as more fully described below).

(c) Following the end of each Performance Period, the Company's Compensation Committee (the "***Committee***") will certify the Company's relative Total Shareholder Return on a percentage rank basis compared to the Comparison Group (the "***Performance Measure***") for such Performance Period (the "***Certification***"). The PRSUs subject to vesting during a Performance Period will be subject to forfeiture and cancellation by the Company if the Company's performance during such Performance Period does not meet or exceed the Threshold Level (as defined in the table set forth in Section 3(a)(iii)) of the Performance Measure for such Performance Period; *provided however*, that such forfeited shares may be subsequently granted subject to the Alternative Three Year Performance Period Vested Unit Calculation. Performance at or above the Threshold Level will result in PRSUs becoming vested as set forth below, and shares underlying such vested PRSUs will be promptly distributed following completion of the Certification but in no event later than March 15 of the year following the year in which the applicable Certification occurred.

(d) Notwithstanding the foregoing, following completion of the three-year period commencing on the Date of Grant and ending on the third anniversary of the Date of Grant (the "***Three Year Performance Period***"), the Committee will determine the number of PRSUs that would vest if the maximum number of PRSUs subject to the Award had been subject only to the Three Year Performance Period (the "***Alternative Three Year Performance Period Vested Unit Calculation***"). If the number of PRSUs that vest pursuant to the Alternative Three Year Performance Period Vested Unit Calculation is greater than the number of PRSUs that vest under this Agreement in the three Performance Periods described herein without regard to the Alternative Three Year Performance Period Vested Unit Calculation, then such greater number of PRSUs will vest pursuant to the Alternative Three Year Performance Period Vested Unit Calculation, reduced by the number of PRSUs previously vested.

2. ADDITIONAL DEFINITIONS.

(a) "***Comparison Group***" means the companies included in the NASDAQ Biotechnology Index on the Date of Grant, as may be adjusted as described in Section 3(b)(iii) below.

(b) "***Performance Period***" means each of the following three periods:

(i) the one-year period commencing on the Date of Grant and ending on the first anniversary of the Date of Grant;

(ii) the two-year period commencing on the Date of Grant and ending on the second anniversary of the Date of Grant; and

(iii) the three-year period commencing on the Date of Grant and ending on the third anniversary of the Date of Grant.

(c) "***Target***" means the target number of shares set forth in the Grant Notice. The Target for each Performance Period will be one-third of the target number of shares set forth in the Grant Notice.

(d) "***Total Shareholder Return***" or "***TSR***" means total shareholder return as applied to the Company or any company in the Comparison Group, meaning stock price appreciation from the beginning to the end of the applicable Performance Period, plus dividends and distributions made or declared (assuming such dividends or distributions are reinvested in the common stock of the Company or any company in the Comparison Group) during the Performance Period, expressed as a percentage return.

3. CALCULATION.

(a) For purposes of the Award, subject to the Negative TSR Cap set forth in Section 3(b)(i) below, the number of PRSUs earned at the end of each Performance Period will be calculated using the method as follows:

(i) First, for the Company and for each other company in the Comparison Group, determine the TSR for the Performance Period.

(ii) Next, rank the TSR values determined in step (i) above from low to high (with the company having the lowest TSR being ranked number 1, the company with the second lowest TSR ranked number 2, and so on) and determine the Company's percentile rank based upon its position in the list by dividing the Company's position by the total number of companies (including the Company) in the Comparison Group and rounding the quotient to the nearest hundredth. For example, if the Company was ranked 60 on the list out of 80 companies (including the Company), its percentile rank would be 75%.

(iii) Finally, plot the percentile rank for the Company determined in accordance with step (ii) above into the appropriate band in the left-hand column of the table below to determine the number of shares earned as a percent of the applicable Target for the applicable Performance Period, which is the figure in the right-hand column of the table below corresponding to that percentile rank. Use linear interpolation between points in the table below to determine the percentile rank and the corresponding share funding if the Company's percentile rank is greater than 25% and less than 75% but not exactly one of the percentile ranks listed in the left-hand column.

	TSR Percentile Rank	**Shares Earned as a Percent of Target**
Maximum Level	75%	150%
	70%	140%
	65%	130%
	60%	120%
	55%	110%
Target Level	50%	100%
	45%	90%
	40%	80%
	35%	70%
	30%	60%
Threshold Level	25%	50%

There is no minimum number of shares or other consideration that you will receive, and no shares will be earned, if the percentile rank is below the 25th percentile in a Performance Period.

(b) Rules of Calculation:

(i) If the Company's absolute TSR is negative over the applicable Performance Period, the pay-out will not exceed 100% of Target for that Performance Period, even if the percentile rank exceeds the 50th percentile (the "***Negative TSR Cap***").

(ii) Except as modified in Section 3(b)(iii) or 3(b)(iv) below, for purposes of computing TSR, the stock price at the beginning of the Performance Period will be the average closing price of a share of common stock over the 20 trading days beginning on the first day of the Performance Period, and the stock price at the end of the Performance Period will be the average closing price of a share of common stock over the 20 trading days preceding and including the last day of the Performance Period, adjusted for changes in capital structure; *provided, however*, that TSR will be negative one hundred percent (-100%) if a company: (A) files for bankruptcy, reorganization, or liquidation under any chapter of the U.S. Bankruptcy Code; (B) is the subject of an involuntary bankruptcy proceeding that is not dismissed within 30 days; (C) is the subject of a stockholder approved plan of liquidation or dissolution; or (D) ceases to conduct substantial business operations.

(iii) Companies will be removed from the Comparison Group if they undergo a Specified Corporate Change. A company that is removed from the Comparison Group before the measurement date will not be included at all in the computation of relative TSR. A company in the Comparison Group will be deemed to have undergone a ***Specified Corporate Change*** *if* it (A) ceases to be a domestically domiciled publicly traded company on a national stock exchange or market system, unless such cessation of such listing is due to a low stock price or low trading volume; (B) has gone private; (C) has reincorporated in a foreign (e.g., non-U.S.) jurisdiction, regardless of whether it is a reporting company in that or another jurisdiction; or (D) has been acquired by another company (whether by a peer company or otherwise, but not including internal reorganizations), or has sold all or substantially all of its assets.

(iv) The Company's Compensation Committee may in its good faith discretion calculate the TSRs and TSR Percentile Rank using a subscription service (such as Bloomberg) provided such calculation is (A) consistently applied, (B) intended to ease the burden of administering this Award, and (C) intended to preserve the overall intent of this Award.

4. VESTING AND TERMINATION OF CONTINUOUS SERVICE.

(a) In General. Subject to the limitations contained herein, your Award will vest, if at all, in accordance with Section 1 above, provided that vesting will cease upon the termination of your Continuous Service except as set forth below. Upon termination of your Continuous Service, the PRSUs that were not vested on the date of such termination will be forfeited at no cost to the Company, and you will have no further right, title or interest in the PRSUs or the shares of Common Stock to be issued in respect of the Award except as set forth below.

(b) Change in Control.

(i) If a Change in Control Termination (as such term is defined in the Company's Severance Benefit Plan adopted October 18, 2018 (the "***Severance Plan***")) occurs during the Change in Control Protection Period (as such term is defined in the Severance Plan), the Award will pay-out at Target and the Target PRSUs subject to such Award that have not already vested will vest immediately upon the Change in Control Termination.

(ii) If a Change in Control (as such term is defined in the Severance Plan) occurs and your Award will not be assumed, continued or substituted by the successor or acquiror entity in such Change in Control, the Award will pay-out at Target and the Target PRSUs subject to such Award that have not already vested will vest immediately upon the Change in Control.

(iii) If a Change in Control (as such term is defined in the Severance Plan) occurs and your Award will be assumed, continued or substituted by the successor or acquiror entity in such Change in Control, the PRSUs subject to such Award will automatically convert upon the Change in Control to time-vested restricted stock units ("***RSUs***") at a rate of one RSU for each of the Target number of PRSUs. The RSUs will not be subject to the relative TSR performance measure described in Section 1 above and instead will vest at Target at the end of the applicable Performance Periods outlined in Section 2(b) above that are still remaining at the time of the Change in Control. Such RSUs will be subject to further acceleration in the case of a Change in Control Termination during the Change in Control Protection Period (as such term is defined in the Severance Plan).

(iv) Notwithstanding anything to the contrary in this Agreement or the Severance Plan, if you are a party to a prior written employment agreement, change of control agreement, or plan or other similar written agreement or plan (each, a "***Prior Agreement***"), that provides, in certain circumstances, for greater benefits regarding the accelerated vesting of equity awards (including PRSUs) following a Change in Control of the Company or similar transaction, the terms of such Prior Agreement shall control the definition of the term "*Change in Control*" (or any term used therein of similar import) and the terms and conditions by which the vesting of the PRSUs may be accelerated as a result of a Change in Control, as well as the benefits that may otherwise be available to you upon a Change in Control.

5. ADJUSTMENTS TO NUMBER OF SHARES.

(a) The number of PRSUs subject to your Award may be adjusted from time to time for Capitalization Adjustments, as provided in the Plan.

(b) Any additional PRSUs that become subject to the Award pursuant to this Section 5 and Section 9, if any, will be subject, in a manner determined by the Board, to the same forfeiture restrictions, restrictions on transferability, and time and manner of delivery as applicable to the other PRSUs covered by your Award.

(c) Notwithstanding the provisions of this Section 5, no fractional shares or rights for fractional shares of Common Stock will be created pursuant to this Section 5. The Board will, in its discretion, determine an equivalent benefit for any fractional shares or fractional shares that might be created by the adjustments referred to in this Section 5.

6. SECURITIES LAW COMPLIANCE. You may not be issued any shares in respect of your Award unless either (i) the shares are registered under the Securities Act; or (ii) the Company has determined that such issuance would be exempt from the registration requirements of the Securities Act. Your Award also must comply with other applicable laws and regulations governing the Award, and you will not receive such shares if the Company determines that such receipt would not be in material compliance with such laws and regulations.

7. TRANSFER RESTRICTIONS. Prior to the time that shares of Common Stock have been delivered to you, you may not transfer, pledge, sell or otherwise dispose of this Award or the shares issuable in respect of your Award, except as expressly provided in this Section 7. For example, you may not use shares that may be issued in respect of your Award as security for a loan. The restrictions on transfer set forth herein will lapse upon delivery to you of shares in respect of your vested Award.

(a) Death. Your Award is transferable by will and by the laws of descent and distribution. In addition, upon receiving written permission from the Board or its duly authorized designee, you may, by delivering written notice to the Company, in a form provided by or otherwise satisfactory to the Company and any broker designated by the Company to effect transactions under the Plan, designate a third party who, in the event of your death, will thereafter be entitled to receive any distribution of Common Stock or other consideration to which you were entitled at the time of your death pursuant to this Agreement. In the absence of such a designation, your executor or administrator of your estate will be entitled to receive, on behalf of your estate, such Common Stock or other consideration.

(b) Certain Trusts. Upon receiving written permission from the Board or its duly authorized designee, you may transfer your Award to a trust if you are considered to be the sole beneficial owner (determined under Section 671 of the Code and applicable state law) while the Award is held in the trust, provided that you and the trustee enter into transfer and other agreements required by the Company.

(c) Domestic Relations Orders. Upon receiving written permission from the Board or its duly authorized designee, and provided that you and the designated transferee enter into transfer and other agreements required by the Company, you may transfer your Award or your right to receive the distribution of Common Stock or other consideration thereunder, pursuant to a domestic relations order that contains the information required by the Company to effectuate the transfer. You are encouraged to discuss the proposed terms of any division of this Award with the Company prior to finalizing the domestic relations order to help ensure the required information is contained within the domestic relations order.

8. DATE OF ISSUANCE.

(a) If the Award is exempt from application of Section 409A of the Code and the regulations and other guidance thereunder and any state law of similar effect (collectively ***"Section 409A"***), the Company will deliver to you a number of shares of the Company's Common Stock equal to the number of vested PRSUs subject to your Award, including any additional PRSUs received pursuant to Section 5 above that relate to those vested PRSUs on the applicable vesting date(s). However, if a scheduled delivery date falls on a date that is not a business day, such delivery date will instead fall on the next following business day. Notwithstanding the foregoing, in the event that (i) you are subject to the Company's policy permitting officers and directors to sell shares only during certain "window" periods, in effect from time to time (the "***Policy***") or you are otherwise prohibited from selling shares of the Company's Common Stock in the public market and any shares covered by your Award are scheduled to be delivered on a day (the "***Original Distribution Date***") that does not occur during an open "window period" applicable to you or a day on which you are permitted to sell shares of the Company's Common Stock pursuant to a written plan that meets the requirements of Rule 10b5-1 under the Exchange Act, in each case as determined by the Company in accordance with the Policy, or does not occur on a date when you are otherwise permitted to sell shares of the Company's Common Stock on the open market, and (ii) the Company elects not to satisfy its tax withholding obligations (if any) by withholding shares from your distribution, then such shares will not be delivered on such Original Distribution Date and will instead be delivered on the first business day of the next occurring open "window period" applicable to you pursuant to such policy (regardless of whether you are still providing Continuous Services at such time) or the next business day when you are not prohibited from selling shares of the Company's Common Stock in the open market, but in no event later than the fifteenth day of the third calendar month of the calendar year following the calendar year in which the shares covered by the Award vest. Delivery of the shares pursuant to the provisions of this Section 8(a) is intended to comply with the requirements for the short-term deferral exemption available under Treasury Regulation 1.409A-1(b)(4) and will be construed and administered in such manner. The form of such delivery of the shares (*e.g.*, a stock certificate or electronic entry evidencing such shares) will be determined by the Company.

(b) The provisions of this Section 8(b) are intended to apply if the Award is subject to Section 409A because of the terms of a severance arrangement or other agreement between you and the Company that provides for acceleration of vesting of the Award upon your separation from service (as such term is defined in section 409A(a)(2)(A)(i) of the Code and applicable guidance thereunder ("***Separation From Service***") and such severance benefit does not satisfy the requirements for an exemption from application of Section 409A provided under Treasury Regulations Sections 1.409A-1(b)(4) or 1.409A-1(b)(9) ("***Non-Exempt Severance Arrangement***"). If the Award is subject to and not exempt from application of Section 409A due to application of a Non-Exempt Severance Arrangement, the following provisions in this Section 8(b) will supersede anything to the contrary in Section 8(a).

(i) If the Award vests in ordinary course during your Continuous Service in accordance with the vesting schedule set forth in the Grant Notice, in no event will the shares to be issued in respect of your Award be issued any later than the later of: (A) December 31st of the calendar year that includes the applicable vesting date, or (B) the 60th day that follows the applicable vesting date.

(ii) If the Award accelerates vesting under the terms of your Non-Exempt Severance Arrangement in connection with your Separation From Service, and such vesting acceleration provisions of your Non-Exempt Severance Arrangement were in effect as of the Date of Grant of the Award and therefore part of the terms of the Award as of the Date of Grant, then the shares will be earlier issued in respect of your Award upon your Separation From Service in accordance with the terms of the Non-Exempt Severance Arrangement, but in no event later than the 60th day that follows the date of your Separation From Service. However, if at the time the shares would otherwise be issued you are subject to the distribution limitations contained in section 409A of the Code applicable to "specified employees" as defined in section 409A(a)(2)(B)(i) of the Code and applicable guidance thereunder, such share issuances will not be made before the date which is six months following the date of your Separation From Service, or, if earlier, the date of your death that occurs within such six month period.

(iii) If the Award accelerates vesting under the terms of your Non-Exempt Severance Arrangement in connection with your Separation From Service, and such vesting acceleration provisions of your Non-Exempt Severance Arrangement were not in effect as of the Date of Grant of the Award and therefore not a part of the terms of the Award on the Date of Grant, then such acceleration of vesting of the Award will not accelerate the issuance date of the shares, but the shares will instead be issued on the same schedule as set forth on the Grant Notice as if they had vested in ordinary course during your Continuous Service, notwithstanding the vesting acceleration of the Award. Such issuance schedule is intended to satisfy the requirements of payment on a specified date or pursuant to a fixed schedule, as provided under Treas. Reg. 1.409A-3(a)(4).

(c) The provisions in this Agreement for delivery of the shares in respect of the Award are intended either to comply with the requirements of Section 409A or to provide a basis for exemption from such requirements so that the delivery of the shares will not trigger the additional tax imposed under Section 409A, and any ambiguities herein will be so interpreted.

9. DIVIDENDS. You will be entitled to receive payments equal to any cash dividends and other distributions paid with respect to a corresponding number of shares to be issued in respect of the PRSUs covered by your Award, provided that if any such dividends or distributions are paid in shares, the Fair Market Value of such shares will be converted into additional PRSUs covered by the Award, and further provided that such additional PRSUs will be subject to the same forfeiture restrictions and restrictions on transferability as apply to the PRSUs subject to the Award with respect to which they relate.

10. RESTRICTIVE LEGENDS. The shares issued in respect of your Award will be endorsed with appropriate legends determined by the Company.

11. AWARD NOT A SERVICE CONTRACT.

(a) Your Continuous Service with the Company or an Affiliate is not for any specified term and may be terminated by you or by the Company or an Affiliate at any time, for any reason, with or without cause and with or without notice. Nothing in this Agreement (including, but not limited to, the vesting of your Award pursuant to Section 1 herein or the issuance of the shares in respect of your Award), the Plan or any covenant of good faith and fair dealing that may be found implicit in this Agreement or the Plan will: (i) confer upon you any right to continue in the employ of, or affiliation with, the Company or an Affiliate; (ii) constitute any promise or commitment by the Company or an Affiliate regarding the fact or nature of future positions, future work assignments, future compensation or any other term or condition of employment or affiliation; (iii) confer any right or benefit under this Agreement or the Plan unless such right or benefit has specifically accrued under the terms of this Agreement or Plan; or (iv) deprive the Company of the right to terminate you at will and without regard to any future vesting opportunity that you may have.

(b) By accepting this Award, you acknowledge and agree that the right to continue vesting in the Award pursuant to Section 1 is earned only by continuing as an employee, director or consultant at the will of the Company (not through the act of being hired, being granted this Award or any other award or benefit) and that the Company has the right to reorganize, sell, spin-out or otherwise restructure one or more of its businesses or Affiliates at any time or from time to time, as it deems appropriate (a "reorganization"). You further acknowledge and agree that such a reorganization could result in the termination of your Continuous Service, or the termination of Affiliate status of your employer and the loss of benefits available to you under this Agreement, including but not limited to, the termination of the right to continue vesting in the Award. You further acknowledge and agree that this Agreement, the Plan, the transactions contemplated hereunder and the vesting schedule set forth herein or any covenant of good faith and fair dealing that may be found implicit in any of them do not constitute an express or implied promise of continued engagement as an employee or consultant for the term of this Agreement, for any period, or at all, and will not interfere in any way with your right or the Company's right to terminate your Continuous Service at any time, with or without cause and with or without notice.

12. WITHHOLDING OBLIGATIONS.

(a) On or before the time you receive a distribution of shares subject to your Award, or at any time thereafter as requested by the Company, you hereby authorize any required withholding (if any) from the Common Stock issuable to you and/or otherwise agree to make adequate provision in cash for any sums required to satisfy the federal, state, local and foreign tax withholding obligations (if any) of the Company or any Affiliate which arise in connection with your Award (the "***Withholding Taxes***"). Additionally, the Company may, in its sole discretion, satisfy all or any portion of the Withholding Taxes obligation relating to your Award by any of the following means or by a combination of such means: (i) withholding from any compensation otherwise payable to you by the Company; (ii) causing you to tender a cash payment; or (iii) withholding shares of Common Stock from the shares of Common Stock issued or otherwise issuable to you in connection with the Award with a Fair Market Value (measured as of the date shares of Common Stock are issued pursuant to Section 8) equal to the amount of such Withholding Taxes; provided, however, that the number of such shares of Common Stock so withheld will not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income.

(b) Unless the tax withholding obligations of the Company and/or any Affiliate are satisfied, the Company will have no obligation to deliver to you any Common Stock.

(c) In the event the Company's obligation to withhold arises prior to the delivery to you of Common Stock or it is determined after the delivery of Common Stock to you that the amount of the Company's withholding obligation was greater than the amount withheld by the Company, you agree to indemnify and hold the Company harmless from any failure by the Company to withhold the proper amount.

(d) If specified in your Grant Notice and permitted by the Company, you may direct the Company to withhold shares of Common Stock with a Fair Market Value (measured as of the date shares of Common Stock are issued pursuant to Section 8) equal to the amount of such Withholding Taxes; provided, however, that the number of such shares of Common Stock so withheld will not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income.

13. UNSECURED OBLIGATION. Your Award is unfunded, and as a holder of a vested Award, you will be considered an unsecured creditor of the Company with respect to the Company's obligation, if any, to issue shares pursuant to this Agreement. You will not have voting or any other rights as a stockholder of the Company with respect to the shares to be issued pursuant to this Agreement until such shares are issued to you pursuant to Section 8 of this Agreement. Upon such issuance, you will obtain full voting and other rights as a stockholder of the Company. Nothing contained in this Agreement, and no action taken pursuant to its provisions, will create or be construed to create a trust of any kind or a fiduciary relationship between you and the Company or any other person.

14. OTHER DOCUMENTS. You hereby acknowledge receipt or the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act, which includes the Plan prospectus. In addition, you acknowledge receipt of the Company's insider-trading policy and agree that you may sell shares only in compliance with such policy, in effect from time to time.

15. NOTICES. Any notices provided for in your Award or the Plan will be given in writing and will be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, five days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. Notwithstanding the foregoing, the Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this Award by electronic means or to request your consent to participate in the Plan by electronic means. You hereby consent to receive such documents by electronic delivery and, if requested, to agree to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

16. MISCELLANEOUS.

(a) The rights and obligations of the Company under your Award will be transferable to any one or more persons or entities, and all covenants and agreements hereunder will inure to the benefit of, and be enforceable by the Company's successors and assigns. Your rights and obligations under your Award may only be assigned with the prior written consent of the Company.

(b) You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your Award.

(c) You acknowledge and agree that you have reviewed your Award in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your Award, and fully understand all provisions of your Award.

(d) This Agreement will be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

(e) All obligations of the Company under the Plan and this Agreement will be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

17. GOVERNING PLAN DOCUMENT. Your Award is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your Award, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. Except as expressly provided herein, in the event of any conflict between the provisions of your Award and those of the Plan, the provisions of the Plan will control.

18. SEVERABILITY. If all or any part of this Agreement or the Plan is declared by any court or governmental authority to be unlawful or invalid, such unlawfulness or invalidity will not invalidate any portion of this Agreement or the Plan not declared to be unlawful or invalid. Any Section of this Agreement (or part of such a Section) so declared to be unlawful or invalid will, if possible, be construed in a manner which will give effect to the terms of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

19. EFFECT ON OTHER EMPLOYEE BENEFIT PLANS. The value of the Award subject to this Agreement shall not be included as compensation, earnings, salaries, or other similar terms used when calculating your benefits under any employee benefit plan sponsored by the Company or any Affiliate, except as such plan otherwise expressly provides. The Company expressly reserves its rights to amend, modify, or terminate any of the Company's or any Affiliate's employee benefit plans.

20. CHOICE OF LAW. The interpretation, performance and enforcement of this Agreement will be governed by the law of the state of California without regard to such state's conflicts of laws rules.

21. AMENDMENT. This Agreement may not be modified, amended or terminated except by an instrument in writing, signed by you and by a duly authorized representative of the Company. Notwithstanding the foregoing, this Agreement may be amended solely by the Board by a writing which specifically states that it is amending this Agreement, so long as a copy of such amendment is delivered to you, and provided that no such amendment adversely affecting your rights hereunder may be made without your written consent. Without limiting the foregoing, the Board reserves the right to change, by written notice to you, the provisions of this Agreement in any way it may deem necessary or advisable to carry out the purpose of the grant as a result of any change in applicable laws or regulations or any future law, regulation, ruling, or judicial decision, provided that any such change will be applicable only to rights relating to that portion of the Award which is then subject to restrictions as provided herein.

22. DISCRETION OF THE COMMITTEE. Unless otherwise explicitly provided herein, the Compensation Committee of the Board of Directors of the Company, or an authorized successor committee thereto, shall make all determinations required to be made hereunder, including but not limited to determinations relating to the achievement of any thresholds or the vesting of any PRSUs hereunder, and shall interpret all provisions of this PRSU Award Agreement and the underlying PRSUs, as it deems necessary or desirable, in its sole and absolute discretion. Such determinations and interpretations shall be binding on and conclusive to the Company and you. Without limiting the foregoing, the Company may, in its sole and absolute discretion, delay payments hereunder or make such other modifications with respect to the issuance of stock hereunder as it reasonably deems necessary to the extent that (a) audited financials are not complete for any applicable period during the Performance Period and/or (b) the Company has not had an adequate opportunity to review the audited financials or confirm the applicable TSR Percentile Ranks.

EXHIBIT 10.46

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 "[***]".

RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT

BETWEEN

ISIS PHARMACEUTICALS, INC.

AND

JANSSEN BIOTECH INC.

RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT

This RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 22nd day of December, 2014 (the "***Effective Date***"), by and between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Isis***"), and **JANSSEN BIOTECH INC.**, a Pennsylvania company, with principal offices located at 800/850 Ridgeview Road, Horsham, PA 19044 ("**JBI**") JBI and Isis each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***." Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in APPENDIX 1. All attached appendices and schedules are a part of this Agreement.

RECITALS

WHEREAS, Isis possesses certain Patent Rights, Know-How, technology and expertise with respect to antisense therapeutics, and has novel and valuable capabilities for the research, discovery, identification, synthesis and development of antisense therapeutics;

WHEREAS, JBI has expertise in developing and commercializing human therapeutics, and JBI is interested in developing and commercializing antisense therapeutics for initially up to three gene targets implicated in Autoimmune Disease (with the right to add a fourth target by paying an additional fee);

WHEREAS, the Parties desire to enter into a collaborative enterprise pursuant to which (i) the Parties will conduct activities directed toward researching, discovering and developing therapeutic antisense oligonucleotides designed to bind and modulate the RNA of each collaboration target, (ii) Isis will endeavor to identify a development candidate for each collaboration target, and (iii) for each collaboration target for which Isis identifies a development candidate, JBI will have an exclusive option to obtain an exclusive license under this Agreement to develop, manufacture and commercialize Products in the Field.

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

ARTICLE 1.
RESEARCH COLLABORATION

1.1 **Collaboration Overview**. The intent of the Collaboration is: (i) for the Parties to conduct a Drug Discovery Program, including formulation activities, for each of the Collaboration Targets and to share their respective expertise to advance the goals set out in the Drug Discovery Plan for each such Drug Discovery Program; (ii) for Isis to generate at least one Development Candidate under each Drug Discovery Program; (iii) for JBI to have an Option to obtain an exclusive license to Develop and Commercialize Products under each Drug Discovery Program in the Field; and (iv) if JBI exercises the Option for a Drug Discovery Program, the Parties will advance the Development Candidate through IND-Enabling Toxicology Studies, and thereafter JBI will continue to Develop and Commercialize the applicable Development Candidate. The purpose of this Section 1.1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement, and therefore this Section 1.1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

1.2 Collaboration Targets.

1.2.1 Maximum Number; Initial Collaboration Target. The maximum number of Collaboration Targets will be three, subject to Section 1.2.2. The Parties agree that the first Collaboration Target is [***]. JBI will designate the second Collaboration Target within [***] of the Effective Date, and designate the third Collaboration Target within [***] of the Effective Date (each, a ***"Target Nomination Period"***), in each case in accordance with the mechanism set forth in Section 1.2.3 below.

1.2.2 Optional Fourth Collaboration Target. JBI will have the right, exercisable within [***] after the Effective Date, to designate a fourth Collaboration Target (*i.e.*, to increase the maximum number of Collaboration Targets by one) in accordance with the mechanism set forth in Section 1.2.3 below upon delivery of written notice thereof to Isis and payment to Isis of the $[***] fee pursuant to Section 6.2, *provided* if JBI exercises such right, JBI must (i) designate such fourth Collaboration Target within [***] after the Effective Date and (ii) JBI may extend the Drug Discovery Term, if necessary, for the time required to execute under a corresponding Drug Discovery Plan for such fourth Collaboration Target under Section 1.5.2. Any [***] shall only become due if the [***], and any [***] shall be [***], and such [***] within [***] days of [***] following the date such Drug Discovery Plan is approved.

1.2.3 Collaboration Target Designation Mechanism. At any time during the applicable Target Nomination Period, JBI may propose a gene target implicated in Autoimmune Disease of the gastro-intestinal tract for designation as a Collaboration Target by providing written notice of such gene target to Isis. Isis may reject a gene target proposed by JBI if, at the time of such proposal: (i) Isis believes in good faith that [***] for such target; (ii) Isis does not have the [***]; (iii) granting a license to such target would [***] to a Third Party and JBI does not [***]; (iv) [***]; (v) the proposed target is the subject of ***] for which Isis in good faith expects to [***] (although Isis will negotiate in good faith terms for JBI to gain access such a program); or (vi) the target is associated with [***] (each of (i) through (vi), a ***"Dispositive Rejection Condition"***). If a Dispositive Rejection Condition for the gene target proposed by JBI for designation as a Collaboration Target exists, Isis may reject the proposed gene target by providing a written notice to JBI by the [***] day following Isis' receipt of JBI's request to designate such gene target as a Collaboration Target, in which event JBI may propose a different gene target for designation as a Collaboration Target using the process described above in this Section 1.2.3.

1.2.4 Collaboration Target Designation. A gene target proposed by JBI for designation as a Collaboration Target in accordance with Section 1.2.3 above will become a "Collaboration Target" if (i) Isis provides JBI a written notice accepting such gene target as a Collaboration Target or (ii) by the [***] day following Isis' receipt of JBI's request to designate such gene target as a Collaboration Target, Isis has not delivered a written notice to JBI rejecting such gene target based on a Dispositive Rejection Condition.

1.2.5 **Substitution of Gene Targets.** At any time prior to completion of [***] activities for a Collaboration Target, JBI may propose, in writing, a substitute gene target to replace such Collaboration Target subject to the following conditions:

i) JBI may propose up to [***] ([***]) substitute gene targets, unless JBI designates a Fourth Collaboration Target whereby, in which case JBI may then propose up to [***] ([***]) substitute gene targets;

ii) JBI shall pay the Substitution Fee for each proposed substitute gene target within [***] ([***]) days of the date the substitute gene target becomes a Collaboration Target under Section 1.2.4; and

iii) The designation mechanism of Section 1.2.3 shall apply for proposed substitute gene targets.

Any gene target substituted out under this Section 1.2.5 will no longer be a Collaboration Target.

1.3 **Drug Discovery and Development Responsibilities**.

1.3.1 **Drug Discovery Programs**. Subject to the terms and conditions of this Agreement, during the Drug Discovery Term, the Parties will jointly conduct collaborative research projects directed to the research, discovery and pre-clinical development of ASOs designed to bind to and modulate the RNA of each Collaboration Target (subject to the applicable maximum number of Collaboration Targets under Section 1.2) (each, a ***"Drug Discovery Program"***).

1.3.2 **Drug Discovery Plans and Development Plans**.

(a) For each Drug Discovery Program, the Parties, via the JRC, will: (i) promptly (but no later than [***] days) following the designation of such Collaboration Target, approve a written plan describing the discovery, research, and optimization activities to be conducted by each Party to achieve [***] status and to identify a Development Candidate, plus any related research activities to support such activities; and (ii) from time to time thereafter, consider and approve appropriate amendments and modifications to such plan (each such plan, as so amended, a ***"Drug Discovery Plan"***). By separate agreement the Parties have agreed upon the initial Drug Discovery Plan for the Drug Discovery Program directed to [***]. Upon JRC approval of the Drug Discovery Plan for any other Collaboration Target, or upon JRC approval of any amendment or modification to any Drug Discovery Plan, the JRC will attach such Drug Discovery Plan, or such amendment or modification (as applicable), to the minutes of the JRC meeting at which the same is approved.

(b) For each Drug Discovery Program with respect to which JBI exercises the Option, JBI will share with Isis, via the JRC (or directly with Isis if the JRC has dissolved) (i) promptly (but no later than [***] days) following such Option exercise, a written plan describing the proposed Development activities to be conducted by JBI with respect to the applicable Development Candidate; and (ii) from time to time thereafter consider and make appropriate amendments and modifications to such plan (each such plan, as so amended, a ***"Development Plan"***). The Parties, at their respective expense, shall meet and confer regarding the activities proposed under the Development Plan and, to the extent there are activities required of Isis under the Development Plan, shall agree on such activities within a reasonable amount of time but not to exceed [***] days following presentation of the Development Plan to the JRC. The JRC will attach such Development Plan or any subsequent amendments or modifications thereto (as applicable) to the minutes of the JRC meeting at which the same is agreed and approved. Each Development Plan will include a description of the pre-clinical studies, and clinical studies (including study designs) to support the further Development of such Development Candidate up to completion of PoC, including [***]. If the Parties agree Isis will conduct any activities to support the further Development of the Development Candidate, the Development Plan will include the specific activities to be performed by Isis and [***] and [***] for completion of such activities. JBI will continue to develop and refine each Development Plan as needed and will submit it to the JRC (or the Parties if the JRC has dissolved) for review and comment at least [***]. When updating each Development Plan, JBI will [***].

1.3.3 **Allocation of Drug Discovery and Development Responsibilities**. Each Drug Discovery Plan and Drug Development Plan will specify the Party(ies) responsible for performing each activity thereunder, and each Party will use Commercially Reasonable Efforts to complete such activities; *provided*, *however*, that unless otherwise mutually agreed by the Parties in writing each Party will use Commercially Reasonable Efforts to complete the following at each respective company's expense unless otherwise indicated:

(a) Isis will be responsible for [***] under each Drug Discovery Plan;

(b) Except as set forth in Sections (c), (d) and (f) of this Section 1.3.3, Isis will be responsible for [***] and [***], in each case to the extent stated to be conducted by Isis in the applicable Drug Discovery Plan;

(c) JBI will be responsible for conducting the (i) [***], and (ii) the [***] including [***], in each case to achieve [***] status and produce the Development Candidate Data Package;

(d) JBI will be responsible for conducting the [***], in each case to achieve [***] status, produce the Development Candidate Data Package, and to support the further Development and Commercialization of Products. Isis will provide [***] if requested by JBI and JBI will pay Isis for such support at [***] and shall invoice JBI in accordance with Section 6.10;

(e) During the Research Term Isis will (i) [***] and (ii) [***], in each case to the extent stated to be conducted by Isis in the applicable Drug Discovery Plan;

(f) JBI will be responsible for conducting [***], including [***]; and

(g) JBI will be responsible for conducting [***] activities for each Development Candidate, including conducting [***], *except* Isis will be responsible for conducting the [***] of the Development Candidate for the first Drug Discovery Program with respect to which JBI exercises the Option (the "***First Development Candidate***") as specified in the applicable Development Plan.

1.3.4 **Conduct of Drug Discovery and Development Plan Activities**. Each Party will perform the activities for which it is responsible under each Drug Discovery Plan and each Development Plan in good scientific manner and in compliance with, as applicable, GLP, GCP and/or GMP, and all Applicable Laws.

1.3.5 **Disclosure of Results**. At least [***] Business Days prior to each regularly scheduled meeting of the JRC, each Party will provide to the JRC a written report (which may take the form of PowerPoint slides) for each Drug Discovery Program (i) describing the Drug Discovery Program activities performed by such Party since the date of the preceding written report delivered by such Party for such Drug Discovery Program and the status of each such activity as of the date of such report and (ii) summarizing the data and results of the Drug Discovery Program activities performed by such Party under the applicable Plan.

1.3.6 **Development Candidate; Supplemental Information**. Isis will notify JBI promptly after designating a Development Candidate and, together with such notice, Isis will provide JBI with the applicable Development Candidate Data Package. During the [***] period beginning on Isis' delivery of the Development Candidate Data Package to JBI, JBI may request in writing additional data or information regarding the Development Candidate of a type that is consistent with the information JBI examines when selecting JBI's own development candidates for similar programs and that JBI in good faith determines is reasonably necessary to inform JBI's decision of whether to exercise the Option for such Drug Discovery Program (the "***Supplemental Information***"); *provided*, *however*, that: (i) unless Isis possesses and can reasonably provide the requested data or information, JBI will be solely responsible for conducting or having conducted by Isis ([***]) the work necessary to generate the requested Supplemental Information and for all agreed upon fees and costs incurred by it or for its account in the performance of such work; (ii) Isis will not be required to conduct any such work unless Isis and JBI agree to a plan for such work and JBI agrees to pay for such work at [***] and for both (i) and (ii) shall invoice JBI in accordance with Section 6.10.

1.3.7 **Records and Quality.** Isis will maintain complete and accurate records of all work Isis conducts in the performance of a Drug Discovery Plan and Development Plan and all results, data, inventions and developments made in the performance of such work. Such records will be in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes. Upon reasonable prior written notice, Isis will provide JBI the right to inspect such records, and will provide copies of all requested records, to the extent reasonably required for the performance of JBI's rights and obligations under this Agreement or for JBI's reasonable quality control purposes. Isis will cooperate in good faith with respect to the conduct of any inspections by any Regulatory Authority of an Isis site or a contractor's site and facilities if such inspection concerns work being performed under a Drug Discovery Plan or Development Plan. [***]. In the event that during an inspection of the Isis facilities, the facilities are found by a Regulatory Authority to be non-compliant with one or more GLP, GMP, GCP or current standards for pharmacovigilance practice compliance standards and such facilities are being used to conduct work under a Drug Discovery Plan or Development Plan, Isis will [***]. If requested by JBI, Isis will allow representatives of JBI to accompany Isis as part of any audit Isis conducts of [***] for which JBI exercises its Option.

1.3.8 **Supply of API for Drug Discovery**. On a Drug Discovery Program-by-Drug Discovery Program basis, Isis will supply (on its own or through a CMO), [***], (i) the non-GMP API necessary for Isis to select up to [***] lead Compounds for each Collaboration Target to advance to [***], plus (ii) up to [***] of non-GMP API for each of the lead Compounds selected for each Collaboration Target to support the formulation work under the Drug Discovery Plan prior to the designation of a Development Candidate. In addition, during the Drug Discovery Term, if requested by JBI, Isis will supply [***] up to [***] of ASO non-GMP API Isis has in its stock as of the Effective Date to support formulation activities under the Drug Discovery Plans, the selection of such non-GMP API to be in Isis' sole discretion. If additional quantities of non-GLP, non-GMP API are necessary to support such Drug Discovery Program activities, then JBI will purchase such API from Isis [***] for such non-GLP, non-GMP API, where [***] and [***] and where [***]. All such API provided by Isis will be [***] specific and [***] specific ASOs. If JBI desires API for ASOs that are specific to [***] then Isis will use Commercially Reasonable Efforts to design and supply such ASOs and JBI will pay Isis for such ASOs [***] and shall invoice JBI in accordance with Section 6.10.

1.3.9 **Supply of GLP Development Candidate and Clinical Supplies by Isis**. For the first Development Candidate for which JBI exercises its Option Isis will (on its own or through a CMO) supply [***] of API, not to exceed [***], to support the [***] and [***], where Isis will supply the [***] of such [***], and will, [***] supply the remainder of such [***] in [***] increments (or in [***] if, as a result of previous [***], the remaining material is [***]) if and when requested by JBI. For each additional Development Candidate for which JBI exercises its Option, Isis, [***], will (on its own or through a CMO) supply in [***] a [***] of API, not to exceed [***], to support the [***] and [***]. Except for the [***] of API for the first Development Candidate for which JBI has exercised its Option, JBI will [***] for such API [***], of which [***] within [***] days of [***]. JBI will take possession of such requested API no later than [***] days following Isis' release of such API.

1.4 **Program Costs and Expenses**. Except as expressly set forth below or elsewhere in this ARTICLE 1, each Party will be responsible for the costs and expenses incurred by it or on its behalf in the performance of the Drug Discovery Program activities for which such Party is responsible under the applicable Drug Discovery Plan and Development Plan.

1.5 **Drug Discovery Term; Extension**.

1.5.1 **Drug Discovery Term**. The term for the conduct of the Drug Discovery Programs will begin on the Effective Date and, subject to extension in accordance with Section 1.5.2 and/or earlier termination of this Agreement in accordance with ARTICLE 10 hereof, will end upon the earlier of (i) such time as the Options with respect to all Drug Discovery Programs either have been exercised by JBI or have expired unexercised, and (ii) the [***] anniversary of the Effective Date (the ***"Drug Discovery Term"***), *provided however*, that if Isis has delivered a Development Candidate Data Package to JBI for a Drug Discovery Program prior to the [***] anniversary of the Effective Date but the Option Period for such Drug Discovery Program has not expired as of the [***] anniversary of the Effective Date, the Drug Discovery Term will extend for that Drug Discovery Program only, until the earlier of (a) JBI's exercise of such Option and (b) expiration of such Option Period. Such extension shall not be subject to the extension fee as defined in Section 1.5.2 below.

1.5.2 **Extension of Drug Discovery Term**. JBI will have the right, in its discretion, to extend the Drug Discovery Term (i) for an additional [***] period if such extension applies to more than just the [***] Collaboration Target (not to exceed [***]), or (ii) for one additional [***] period if such extension only applies to the [***] Collaboration Target (not to exceed [***]), in each case by delivering a written notice of extension to Isis and paying Isis an extension payment of $[***] per extension no later than [***] days prior to the end of the then-applicable Drug Discovery Term.

1.5.3 **Consequences of End of Drug Discovery Term**. From and after the end of the Drug Discovery Term (including any extensions thereof), (i) Isis will have no obligation to perform any further activities for any Drug Discovery Program; (ii) any Drug Discovery Programs that have not reached the Development Candidate stage will no longer be Drug Discovery Programs and the applicable gene targets associated therewith will no longer be Collaboration Targets; (iii) Isis' obligations and JBI's rights under this Agreement with respect to such gene target and any ASOs targeting such gene target will then terminate, and Isis will be free to Develop and Commercialize on its own or with a Third Party such gene target and any Compounds targeting such gene target; and (iv) Isis will own any data generated under the Drug Discovery Program for such gene target and any Compounds targeting such gene target. For clarity, except to the extent explicitly set forth in the foregoing, the expiration of the Drug Discovery Term will not affect either Party's rights or obligations under this Agreement with respect to any Drug Discovery Program for which JBI exercised its Option before the end of the Drug Discovery Term, including, but not limited to, the Parties' respective rights and obligations under ARTICLE 2, ARTICLE 4, ARTICLE 5 and ARTICLE 6 hereof.

1.5.4 **Carryover Development Candidates**. If, despite Isis' Commercially Reasonable Efforts, by the end of the Drug Discovery Term, Isis has not designated a Development Candidate for a particular Drug Discovery Program, then if at any time during the [***] following the end of the Drug Discovery Term Isis' RMC designates an ASO discovered by Isis that is designed to bind to the RNA that encodes the Collaboration Target that was the subject of such Drug Discovery Program as a development candidate ready to start IND-Enabling Toxicology Studies (such ASO, a ***"Carryover Development Candidate"***), then, Isis will notify JBI and will provide JBI with the data package presented to Isis' RMC to approve such Carryover Development Candidate. JBI will then have [***] days from its receipt of such package to elect to enter into an agreement (or amendment to this Agreement) for an option and license under the same terms as set forth in this Agreement, including the payment of the fee for [***] if not already paid by JBI (except that no additional option fee under Section 6.1 will be due). If, within [***] days after JBI's receipt of such notice from Isis, JBI provides Isis with written notice that it accepts such offer from Isis for such Carryover Development Candidate, the Parties will execute an agreement (or amendment to this Agreement) regarding such Carryover Development Candidate containing the same terms as those described herein. If JBI either notifies Isis that it declines the offer for such Carryover Development Candidate, or JBI does not provide Isis with written notice during such [***]-day period that JBI accepts such offer from Isis for such Carryover Development Candidate, then Isis will be free to research, develop, manufacture and commercialize such Carryover Development Candidate (and/or any other ASO designed to bind to the RNA that encodes the gene target targeted by such Carryover Development Candidate) by itself or with or for a Third Party.

1.6 **Program Management**.

1.6.1 **JRC**. The Parties will establish a joint research committee (the "***JRC***") to provide advice and make recommendations on the conduct of activities under each Drug Discovery Program. The JRC will consist of three representatives appointed by Isis and three representatives appointed by JBI. Each JRC member will be a senior scientific staff leader or have other experience and expertise appropriate for the stage of development of the Drug Discovery Programs. Each Party will designate one of its two representatives who is empowered by such Party to make decisions related to the performance of such Party's obligations under this Agreement to act as the co-chair of the JRC. The co-chairs will be responsible for overseeing the activities of the JRC consistent with the responsibilities set forth in Section 1.6.2. SCHEDULE 1.6.1 sets forth certain JRC governance matters agreed to as of the Effective Date. The JRC will determine the JRC operating procedures at its first meeting, including the JRC's policies for replacement of JRC members, policies for participation by additional representatives or consultants invited to attend JRC meetings, and the location of meetings, which will be codified in the written minutes of the first JRC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending JRC meetings.

1.6.2 **Role of the JRC**. Without limiting any of the foregoing, subject to Section 1.6.3, the JRC will perform the following functions, some or all of which may be addressed directly at any given JRC meeting:

(a) maintain the list of Collaboration Targets, as such list may be updated from time to time in accordance with this Agreement, and attach such list to the minutes of the next JRC meeting following the designation of any additional Collaboration Target;

(b) review and approve the Drug Discovery Plan for each Program;

(c) review the overall progress of the Parties' efforts to achieve [***] with respect to each Drug Discovery Program;

(d) review the overall progress of Isis' efforts to discover, identify, optimize and select the Development Candidate for each Drug Discovery Program;

(e) review the overall progress of the Parties' efforts with respect to each the Drug Discovery Plan;

(f) amend each Drug Discovery Plan for each Drug Discovery Program,

(g) such other review and advisory responsibilities as may be assigned to the JRC pursuant to this Agreement.

1.6.3 **Decision Making**. Each Party will give due consideration to, and consider in good faith, the recommendations and advice of the JRC regarding the conduct of each Drug Discovery Program. Subject to Section 1.3.1 and Section 1.3.5, (i) Isis will have the final decision-making authority regarding [***] and whether to accept and how to implement the JRC's recommendations, and (ii) JBI will have the final decision-making authority regarding [***]; *provided that*, in each case, such decisions and conduct are in accordance with the applicable Drug Discovery Plan and do not increase the cost of the other Party. Except as otherwise permitted by Section 1.3.2, Section 1.3.5 and, the JRC will have no decision making authority and will act as a forum for sharing information about the activities conducted by the Parties hereunder and as an advisory body, in each case only on the matters described in, and to the extent set forth in, this Agreement.

1.6.4 **Term of the JRC**. Isis' obligation to participate in the JRC, or any of its subcommittees, will terminate upon JBI's exercise (or expiration) of the Option for the last Drug Discovery Program.

1.6.5 **Alliance Managers**. Each Party will appoint a representative to act as its alliance manager under this Agreement (each, an "***Alliance Manager***"). Each Alliance Manager will be responsible for supporting the JRC and performing the activities listed in SCHEDULE 1.6.5.

1.6.6 **Information Sharing Committee.** Formation and Purpose: Within [***] days after the [***], the Parties will establish an Information Sharing Committee (the "ISC") to review the Development of Product. The ISC will review and discuss the Development activities to be undertaken with respect to the Product being Developed by JBI and will provide a forum for Isis to provide input into such Development activities. Specific Responsibilities of the ISC: As part of its overall responsibilities, the ISC will: review the progress of the Development Plan; review any changes to the Development Plan; actively seek Isis input and consider all input in good faith; and perform such other functions as appropriate to further the purposes of this Agreement as determined by the Parties

1.6.7 **ISC Meetings**: The ISC will meet at least annually or on an *ad hoc* basis. The first meeting of the ISC will be held as soon as reasonably practicable, but in no event later than [***] days after formation. Meetings will be held at such place or places as are mutually agreed or by teleconference or videoconference. The ISC meetings will be chaired by JBI. The chairperson of the ISC will be responsible for calling meetings, preparing and circulating an agenda in advance of each meeting of the ISC, and preparing and issuing minutes of each meeting within [***] days thereafter; provided however, that an ISC chairperson will call a meeting promptly upon the request by Isis to convene an ISC meeting. The minutes will not be finalized until both Parties review and approve them. Each Party will bear its own costs, including travel expenses, incurred by its ISC members or by any additional non-member participants of a Party in connection with their attendance at ISC meetings and other activities related to any ISC. Notwithstanding Section 1.6.6 and the foregoing provisions of this Section 1.6.7, with respect to Isis, the formation of the ISC and participation in the ISC are rights but not obligations that Isis may cancel for any Product at any time.

1.6.8 **Reduction of ISC Reporting**. If JBI declines to pursue any Follow-On Compounds targeting a particular Collaboration Target and Isis pursues a Follow-On Compound for such Collaboration Target, the ISC shall cease all ISC reporting activities relating to Products that modulate such Collaboration Target.

1.7 **Materials Transfer.** To facilitate the activities under the Drug Discovery Programs, either Party may provide certain materials for use by the other Party. All such materials will be used by the receiving Party in accordance with terms of this Agreement solely for purposes of exercising its rights and performing its obligations under this Agreement, and the receiving Party will not transfer such materials to any Third Party except with the written consent of the supplying Party. Except as expressly set forth herein, THE MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

ARTICLE 2.
EXCLUSIVITY COVENANTS

2.1 Exclusivity; Right of First Negotiation.

2.1.1 Exclusivity Covenants.

(a) **The Parties' Exclusivity Covenants for Collaboration Targets During the Option Period**. On a Collaboration Target-by-Collaboration Target basis, each Party agrees that, except in the performance of its obligations under this Agreement and except as set forth in Section 2.1.2, Section 2.1.3, Section 10.3.2 or Section 10.3.4, it will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to discovery, research, development, manufacture or commercialization of an ASO that is designed to bind to the RNA that encodes such Collaboration Target in the Field from the Effective Date through the expiration of the applicable Option Period or the earlier termination of the applicable Option.

(b) **Isis' Exclusivity Covenant After Option Exercise**. On a Collaboration Target-by-Collaboration Target basis, except as set forth in Section 2.1.2, Section 2.1.3, Section 10.3.2 or Section 10.3.4, if JBI exercises the Option in accordance with this Agreement, then Isis will not work independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party) with respect to:

(i) discovery, research or development of an ASO that is designed to bind to the RNA that encodes such Collaboration Target in the Field until [***] for a Product targeting such Collaboration Target; and

(ii) on a country-by-country basis, commercializing an ASO that is designed to bind to the RNA that encodes such Collaboration Target in the Field until [***] with respect to such Collaboration Target.

(c) **JBI's Exclusivity Covenant After Option Exercise**. After Option exercise, JBI's exclusivity obligations under Section 2.1.1(a) will be extended and will continue for so long as and to the extent of Isis' exclusivity obligations under Section 2.1.1(b), and except as otherwise described in Section 2.1.3.

2.1.2 Right of First Negotiation for Follow-On Compounds. On a Drug Discovery Program-by-Drug Discovery Program basis, during the period commencing on the date JBI exercises the applicable Option in accordance with this Agreement and ending upon [***] (such period, the "***ROFN Period***"), Isis hereby grants to JBI a right of first negotiation to develop and commercialize any Follow-On Compound developed by or on behalf of Isis, which right of first negotiation is granted on the following terms and conditions:

(a) At any time prior to the [***] following the [***] for the applicable Product, JBI may provide Isis with a non-binding, good faith written notice expressing JBI's desire for Isis to identify a Follow-On Compound (a "***Follow-On Interest Notice***"). If (i) JBI does not provide Isis with a Follow-On Interest Notice before the [***] following the [***] for the applicable Product, or (ii) JBI does timely provide Isis with a Follow-On Interest Notice but the Parties do not agree on a [***] related to such Follow-On Compound by 5:00 pm (Eastern Time) on the [***] following the [***] for the applicable Product, then, Isis may work independently or with any of its Affiliates or any Third Party with respect to the discovery, research, development and manufacture of a Follow-On Compound; *provided, however*, that during [***], Isis will not grant any license (or an option to obtain such a license) under any intellectual property owned, controlled or licensed by Isis to make, use or sell any Follow-On Compound (a "***Follow-On Agreement***") *unless and until* Isis provides a written notice to JBI (a "***Follow-On Negotiation Notice***"), which notice [***]. Isis will not enter into such a Follow-On Agreement with any Third Party until the earlier to occur of: (A) [***] (each, a "***ROFN Termination Event***").

(b) Following a ROFN Termination Event, subject to JBI's right under Section 1.6.8 to stop sharing information, Isis will have no further obligation to negotiate with JBI or its Affiliates with respect to such Follow-On Agreement, and Isis will be free to negotiate and enter an agreement with a Third Party with respect to a Follow-On Agreement. Any Follow-On Agreement entered into by Isis with a Third Party in accordance with this Section 2.1.2(b) will be a Permitted License to the extent related to the Follow-On Compound.

2.1.3 **Limitations and Exceptions to Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, each Party's practice of the following will not violate Section 2.1.1 and/or Section 2.1.2:

(a) Any activities conducted pursuant to the Prior Agreements as in effect on the Effective Date; provided, [***];

(b) The granting by Isis of, or performance of obligations under, Permitted Licenses;

(c) Up to and including the date of the [one year anniversary following the Option Period for a designated Collaboration Target, JBI may acquire, by license or otherwise, any Third Party asset that modulates a Collaboration Target so long as such Third Party asset has at least entered a Phase II Clinical Trial at the time of such acquisition; and

(d) After the date of the [***] for a designated Collaboration Target, JBI may [***], any Third Party [***] so long as such Third Party [***].

2.2 **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the RNA that encodes a Collaboration Target in the Field with the intent of treating Autoimmune Diseases of the gut. Isis and JBI are subject to exclusivity obligations under Section 2.1; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party) may continue to discover, research, develop, manufacture and commercialize products that are designed to bind to the RNA that encodes any gene that is *not* a Collaboration Target for any indication, even if such products are designed to treat Autoimmune Disease.

ARTICLE 3.
EXCLUSIVE OPTION

3.1 **Option Grant and Option Deadline**. On a Drug Discovery Program-by-Drug Discovery Program basis, Isis hereby grants to JBI with respect to each Drug Discovery Program an exclusive option to obtain the license set forth in Section 4.1.1 with respect to such Drug Discovery Program (each an "***Option***"). JBI (i) shall provide Isis with written notice of its intent to exercise its Option within [***] days of receipt of the Development Candidate package for the application Drug Discovery Program and (ii) JBI shall pay the Option Fee described in Section 6.4 no later than the [***] day following JBI's notice of its intent to exercise its Option (the "***Option Deadline***").

3.2 **Effect of Option Exercise or Expiration**. If, by the Option Deadline, JBI or its designated Affiliate (i) notifies Isis in writing that it wishes to exercise the applicable Option, and (ii) pays to Isis the license fee set forth in Section 6.4, Isis will, and hereby does, grant to JBI or its designated Affiliate the license set forth in Section 4.1.1. If, by the applicable Option Deadline, JBI or its designated Affiliate has not both (y) provided Isis a written notice stating that JBI is exercising its Option, and (z) paid Isis the license fee in accordance with Section 6.4, then JBI's Option for the applicable Drug Discovery Program will expire.

ARTICLE 4.
LICENSE GRANTS

4.1 **License Grants to JBI**.

4.1.1 **Development and Commercialization License**. Subject to the terms and conditions of this Agreement, on a Drug Discovery Program-by-Drug Discovery Program basis, effective upon JBI's exercise of the Option for a particular Drug Discovery Program in accordance with this Agreement, Isis grants to JBI (i) a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Isis Product Specific Patents to Research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize Products under such Drug Discovery Program in the Field, and (ii) a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology other than the Isis Product Specific Patents to Research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize Products under such Drug Discovery Program in the Field. The grant described in subsection (ii) in no way limits Isis' ability to grant additional licenses to Third Parties under the Licensed Technology, other than the Isis Product Specific Patents, to Research, Develop, Manufacture, have Manufactured register, market and Commercialize Third Party products that are not Product(s).

4.1.2 Sublicense Rights; CMO Licenses.

(a) Subject to the terms and conditions of this Agreement, JBI will have the right to grant sublicenses under the license granted under Section 4.1.1 above:

(i) under the Isis Core Technology Patents, Isis Product-Specific Patents, Isis Formulation Patents and Isis Know-How, to an Affiliate of JBI or a Third Party; and

(ii) under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How, solely to (y) [***] or (z) [***];

provided that each such sublicense will be subject to, and consistent with, the terms and conditions of this Agreement. If, within 90 days of first learning of any breach of such sublicense terms, JBI fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.1.2, which failure would cause an adverse effect on Isis, JBI hereby grants Isis the right to enforce such sublicense terms on JBI's behalf and will cooperate with Isis (which cooperation will be at JBI's sole expense and will include, JBI joining any action before a court or administrative body filed by Isis against such Sublicensee if and to the extent necessary for Isis to have legal standing before such court or administrative body) in connection with enforcing such terms. JBI will provide Isis with a true and complete copy of any sublicense granted pursuant to this Section 4.1.2 within [***] days after the execution thereof.

(b) In connection with [***], or supply API and Finished Drug Product for Commercialization, Isis will, at JBI's option, either (1) [***], which Isis agrees it will [***], or, (2) permit JBI to [***]. Each such manufacturing agreement between JBI and [***] will contain provisions permitting Isis to elect to have such agreements assigned to Isis to the extent such agreement relates to the applicable Clinical Supplies or Finished Drug Product in the event of a termination of this Agreement with respect to a particular Drug Discovery Program. JBI will provide Isis with a true and complete copy of any manufacturing agreement entered into with [***] within [***] days after the execution thereof. Notwithstanding the foregoing, if Isis fails to comply with the terms of this Section 4.1.2(b) and does not cure such failure within [***] days after written notice from JBI specifying the details of any such failure, JBI will have the right to grant a sublicense under the Isis Manufacturing and Analytical Patents and Isis Manufacturing and Analytical Know-How to [***].

(c) **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, any Sublicensee will, from the effective date of such termination, automatically become a direct licensee of Isis with respect to the rights sublicensed to the Sublicensee by JBI; *so long as* (i) such Sublicensee is not in breach of its sublicense agreement, (ii) such Sublicensee agrees in writing to comply with all of the terms of this Agreement to the extent applicable to the rights originally sublicensed to it by JBI, and (iii) such Sublicensee agrees to pay directly to Isis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by JBI. JBI agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Isis and if requested, the Sublicensee.

4.1.3 **No Implied Licenses**. All rights in and to Licensed Technology not expressly licensed to JBI under this Agreement are hereby retained by Isis or its Affiliates. All rights in and to JBI Technology not expressly licensed or assigned to Isis under this Agreement, are hereby retained by JBI or its Affiliates. Except as expressly provided in this Agreement, no Party will be deemed by estoppel or implication to have granted the other Party any license or other right with respect to any intellectual property.

4.1.4 **License Conditions; Limitations**. Subject to Section 6.9, any license granted under Section 4.1.1 and the sublicense rights under Section 4.1.2 are subject to and limited by (i) any applicable Third Party Obligations, (ii) the Prior Agreements, and (iii) the Isis In-License Agreements, in each case to the extent the provisions of such obligations or agreements are specifically disclosed to JBI in writing (or via electronic data room) prior to JBI's exercise of the applicable Option. Isis will disclose to JBI any Third Party Obligations Isis believes apply to applicable Products each time [***], and JBI will have the right to elect to exclude any Third Party Patent Rights and Know-How to which such Third Party Obligations apply by providing Isis written notice prior to Option exercise. If, prior to an Option exercise, JBI provides Isis with such a written notice to exclude certain Third Party Patent Rights and Know-How, such Third Party Patent Rights and Know-How will not be included in the Licensed Technology licensed with respect to the applicable Products under this Agreement. If JBI does not provide Isis with such a written notice to exclude such Third Party Patent Rights and Know-How prior to an Option exercise, such Third Party Patent Rights and Know-How (and any Third Party Obligations to the extent applicable to Products) will be included in the Licensed Technology licensed with respect to the applicable Products under this Agreement.

4.1.5 **Trademarks for Products**. JBI or its designated Affiliate will be solely responsible for developing, selecting, searching, registering and maintaining, and, subject to Section 10.3, will be the exclusive owner of, all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products.

4.2 **Assignment of Isis Product-Specific Patents; Grant Back to Isis**.

4.2.1 After JBI has (a) exercised its Option for a particular Product and obtained the license under Section 4.1.1, and (b) [***], then following review and consideration by each Party's patent representatives, Isis will assign to JBI or one or more of its designated Affiliates, Isis' ownership interest in (i) all Isis Product-Specific Patents related to such Product in the Field that are owned by Isis (whether solely owned or jointly owned with one or more Third Parties), and (ii) any Jointly-Owned Program Patents Covering such Product, and thereafter, subject to Section 7.2.4, Isis will have no further right to control any aspect of the Prosecution and Maintenance of such Isis Product Specific Patents and such Jointly-Owned Program Patents. The assignment of Patent Rights assigned in this Section 4.2.1 will occur within 30 days of JBI paying Isis the milestone for Completion of a PoC for the applicable Product.

4.2.2 JBI grants to Isis a fully-paid, royalty-free, worldwide, exclusive, sublicensable license under any Isis Product Specific Patents and Jointly-Owned Program Patents assigned to JBI under Section 4.2.1, (i) [***], (ii) to [***] and (iii) to [***] to the extent permitted by this Agreement.

4.3 **Subcontracting**. Subject to the terms of this Section 4.3, each Party will have the right to engage Third-Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor to be engaged by a Party to perform a Party's obligations set forth in the Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity and will enter into such Party's standard nondisclosure agreement consistent with such Party's standard practices. Any Party engaging a subcontractor hereunder will remain responsible and obligated for such activities and will not grant rights to such subcontractor that interfere with the rights of the other Party under this Agreement.

4.4 **Technology Transfer after Option Exercise**. On a Drug Discovery Program-by-Drug Discovery Program basis, Isis will promptly, but no later than [***] days after JBI exercises its Option for such Drug Discovery Program hereunder, deliver to JBI or one or more designated Affiliates:

4.4.1 **Isis Know-How**. All Isis Know-How in Isis' possession that has not previously been provided hereunder, for use solely in accordance with the licenses granted under Section 4.1.1 and Section 10.3.2, including transferring the IND for the applicable Development Candidate to JBI together with all regulatory documentation (including drafts) related to the applicable Development Candidate.

4.4.2 **Isis Manufacturing and Analytical Know-How**. Solely for use by JBI, its Affiliates or a Third Party acting on JBI's behalf to Manufacture API in JBI's own or an Affiliate's manufacturing facility, all Isis Manufacturing and Analytical Know-How in Isis' Control relating to applicable Products, which is necessary for the exercise by JBI, its Affiliates or a Third Party of the Manufacturing rights granted under Section 4.1.1, in each case solely to Manufacture API, Clinical Supplies or Finished Drug Product in accordance with the terms of this Agreement.

4.4.3 **Isis Contribution of FTEs for Know-How Transfer.** Isis will provide up to [***] hours of its time [***] to JBI for each Drug Discovery Program to transfer such Isis Know-How and Manufacturing and Analytical Know-How under Section 4.4.1 and Section 4.4.2. Thereafter, if requested by JBI, Isis will provide JBI with a reasonable level of assistance in connection with such transfer, which JBI will reimburse Isis for its time incurred in providing such assistance at [***] incurred by Isis in providing such assistance and shall invoice JBI in accordance with Section 6.10.

4.4.4 **API and Product**. Upon JBI's written request, Isis will sell to JBI any bulk API in Isis' possession at the time of Option exercise, at a price equal to [***].

4.5 **Cross-Licenses Under Program Technology.**

4.5.1 **Enabling Patent Licenses from JBI to Isis.** Subject to the terms and conditions of this Agreement (including Isis' exclusivity obligations under Section 2.1.1), JBI hereby grants Isis a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicenseable license under any JBI Program Technology to research, develop, manufacture, have manufactured and commercialize [***].

4.5.2 **Enabling Patent Licenses from Isis to JBI.** Subject to the terms and conditions of this Agreement (including JBI's exclusivity obligations under Section 2.1.1), Isis hereby grants JBI a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicenseable license under any Isis Program Technology to research, develop, manufacture, have manufactured and commercialize [***].

ARTICLE 5.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1 **JBI Diligence**. Following an Option exercise, JBI will be solely responsible for all Development, Manufacturing and Commercialization activities, and for all costs and expenses associated therewith, with respect to the Development, Manufacture and Commercialization of applicable Products; and JBI will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize in each and every Major Market at least one Product from each Drug Discovery Program for which an Option has been exercised.

5.2 **Specific Performance Milestone Events**. Without limiting any of the foregoing, following an Option exercise, JBI will use Commercially Reasonable Efforts to achieve the specific performance milestone events set forth in SCHEDULE 5.2 ("***Specific Performance Milestone Events***") for a Product on the timeline set forth in SCHEDULE 5.2; *provided*, *however*, if [***].

5.3 **Integrated Development Plan**. On a Product-by-Product basis, JBI will prepare a Development and global integrated Development plan outlining key aspects of the Development of each Product through Approval (each, an "***Integrated Development Plan***" or "***IDP***"). JBI will prepare the IDP no later than [***] after [***], and the IDP will contain information consistent with JBI's Development plans for its similar products at similar stages of development. Once JBI has prepared such plans, JBI will update the IDP consistent with JBI's standard practice and provide such updates to Isis annually via the ISC.

5.4 **Regulatory**.

5.4.1 **Ownership of and Assistance with Regulatory Filings**.

(a) For each Product for which JBI has exercised its Option, JBI will be the sponsor and will be responsible for filing the IND. Once a Development Candidate is designated under this Agreement, the JRC will work to establish a plan for IND filing support and activities, which plan will include a timeline and responsibilities for filing the IND.

(b) [***] begin to prepare a plan, for drafting and reviewing the sections of the NDA and MAA for the applicable Product (including establishing responsibilities for drafting and reviewing common technical document ("***CTD***") modules, authorship, plan activity timelines and associated costs and expenses). The Parties will act in good faith and mutually agree upon each such plan, *provided, however*, that, after exercising an Option for the applicable Drug Discovery Program, JBI will have final decision making authority with respect to the contents of such plan that do not require Isis' participation.

(c) [***] regulatory filings for the Product, [***] and JBI, including [***] plus any reasonable ***] providing such assistance and will specify that JBI will [***] designated responsibilities in connection with the applicable regulatory filing [***] in accordance with Section [***]; provided there will be no additional ***] conducted under a Development Plan where [***].

5.4.2 **[***] Meetings with FDA**. For each Product, JBI shall [***] meetings with the FDA to discuss (i) pre-IND filing matters; (ii) end of Phase II matters; or (iii) pre-NDA filing matters. [***].

5.4.3 **[***] Regulatory Meetings**. JBI will [***] of any meetings JBI has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product or that directly relate to ***], and may allow [***]. In addition, JBI will provide Isis with as much advance written notice as practicable of any [***] Regulatory Authorities, and JBI [***].

5.4.4 **Regulatory Communications**. [***], JBI [***] provide Isis with copies of documents and communications submitted to, or received from, Regulatory Authorities [***] that materially impact the Development or Commercialization of Products for [***], and JBI will [***] such documents and communications.

5.4.5 **Class Generic Claims**. To the extent JBI intends to make any claims in a Product label or regulatory filing that are class generic to ASOs, JBI will provide such claims and regulatory filings to Isis in advance and will consider in good faith any proposals and comments made by Isis.

5.4.6 **End of Obligations if [***]**. JBI's obligations under Section 5.4.2, Section 5.4.3, and Section 5.4.4 will cease with respect to a particular Product if [***].

5.5 **Applicable Laws**. JBI will use commercially reasonable efforts perform its activities pursuant to this Agreement in compliance with GLP, GCP and GMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

5.6 **Isis' Antisense Safety Database**.

(a) JBI will provide Isis with copies of [***] and the [***] within [***] days following the date such information is [***], as applicable. JBI will [***]. All such information disclosed by JBI to Isis will be JBI Confidential Information. JBI will deliver all such information to Isis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Isis). JBI will also cause its Affiliates and Sublicensees to comply with this Section 5.6(a).

(b) During the term of this Agreement, if requested by JBI, JBI and Isis will [***].

ARTICLE 6. FINANCIAL PROVISIONS

6.1 **Option Fee**. In partial consideration for JBI's Options hereunder, within five Business Days following the Effective Date, JBI will pay Isis an Option fee equal to $10,000,000 for each of the three Drug Discovery Programs for an aggregate payment of $30,000,000.

6.2 **Fourth Target Fee**. If JBI elects to designate a fourth target, JBI will pay Isis $[***] within [***] days of JBI's written notice to Isis designating such target.

6.3 **Milestone Payments for Achievement of Pre-Licensing Milestone Event**. As further consideration for JBI's Options and Licenses hereunder, on a Collaboration Target-by-Collaboration Target basis, JBI will pay to Isis a milestone payment of $[***] for achievement of [***] for such Collaboration Target (each, a "***Pre-Licensing Milestone Event***"). Isis shall provide JBI with written notice of achievement of [***] and JBI shall make such payment within [***] days of receipt of such notification. With respect to [***], the Parties agree that [***] is deemed to have been achieved so that Isis may [***], and JBI will make the associated payment under this Section 6.3 within [***] days of the Effective Date; provided such payment does not limit the Parties' obligation to conduct the activities set forth in the Drug Discovery Plan for [***].

6.4 **License Fee**. On an Option-by-Option basis, together with JBI's written notice to Isis stating that JBI is exercising the Option with respect to the Drug Discovery Program for a Collaboration Target in accordance with this Agreement, JBI will pay to Isis the applicable one-time license fee set forth in TABLE 1 below (each, a "***License Fee***"):

TABLE 1	
Option	**License Fee**
[***]	$[***]
[***]	$[***]

6.5 **Milestone Payments for Achievement of Post-Licensing Milestone Events**. On a Drug Discovery Program-by-Drug Discovery Program basis, JBI will pay to Isis the applicable milestone payment set forth in TABLE 2 below for the first achievement of the corresponding milestone event in TABLE 2 (each, a "***Post-Licensing Milestone Event***") by the first Product against such Collaboration Target to achieve such Post-Licensing Milestone Event:

TABLE 2	
Post-Licensing Milestone Event	**Milestone Event Payment**
[***]	$[***]
[***]	$[***]
[***]*	$[***]*
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]

*[***].

6.6 **Limitations on Milestone Payments; Exceptions; Notice**.

6.6.1 Each milestone payment set forth in TABLE 2 above will be paid only once per Drug Discovery Program upon the first achievement of the applicable Post-Licensing Milestone Event, regardless of how many Products under a Drug Discovery Program achieve such Milestone Event.

6.6.2 If a particular Post-Licensing Milestone Event is not achieved because Development activities transpired such that achievement of such earlier Milestone Event was unnecessary or did not otherwise occur, then upon achievement of the next Post-Licensing Milestone Event to be achieved, the Post-Licensing Milestone Event payment applicable to such earlier Post-Licensing Milestone Event will also be due. For example, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] Milestone Event, both the [***] and [***] Milestone Event payments are due.

6.6.3 Each time a Post-Licensing Milestone Event is achieved under this ARTICLE 6, JBI will send Isis, or Isis will send JBI, as the case may be, a written notice thereof promptly (but no later than [***]) following the date of achievement of such Milestone Event, and such payment will be due within [***] of the date such notice was delivered.

6.7 **Net Sales Milestone Payments**. On a Drug Discovery Program-by-Drug Discovery Program basis, for the first Calendar Year in which Annual worldwide Net Sales of the first Product progressed from a Drug Discovery Program that achieves or exceeds each of the levels of Annual worldwide Net Sales set forth in TABLE 3 below (each, a "***Sales Milestone Event***"), JBI will pay Isis the corresponding one-time Sales Milestone Event payment within [***] days of the end of the Calendar Quarter during such Calendar Year in which such Sales Milestone Event occurs.

TABLE 3

Annual Worldwide Net Sales	Sales Milestone Event Payment
≥ $[***]	$[***]
≥ $[***]	$[***]
≥ $[***]	$[***]

Each Sales Milestone Event payment set forth in TABLE 3 above will be due only one time per Drug Discovery Program, for the first Calendar Year in which the corresponding Sales Milestone Event occurs. If more than one of the above Sales Milestone Events is achieved in the same year, JBI will pay all applicable milestone payments.

6.8 Royalty Payments to Isis.

6.8.1 JBI Royalty. As partial consideration for the rights granted to JBI hereunder, subject to the provisions of this Section 6.8.1 and Section 6.8.2, JBI will pay to Isis royalties on a Product-by-Product basis, on Annual worldwide Net Sales of Products included in the applicable Drug Discovery Program sold by JBI, its Affiliates or Sublicensees, on a country-by-country basis, in each case in the amounts as follows in TABLE 4 below (the "***JBI Royalty***"):

TABLE 4

Royalty Tier	Annual Worldwide Net Sales of Products	Royalty Rate
1	For the portion of Annual Worldwide Net Sales < $[***]	[***]%
2	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%
3	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%

(a) Annual worldwide Net Sales will be calculated by [***].

(b) For purposes of clarification, any Isis Product-Specific Patents and Jointly-Owned Program Patents assigned to JBI as set forth in Section 4.2.1 will still be royalty-bearing and considered Isis Product-Specific Patents and Jointly-Owned Program Patents, respectively, for determining the royalty term and applicable royalty rates under this ARTICLE 6.

6.8.2 Application of Royalty Rates. All royalties set forth under Section 6.8.1 are subject to the provisions of this Section 6.8.2, and are payable as follows:

(a) **Royalty Period**. JBI's obligation to pay Isis the JBI Royalty above with respect to Products will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product in a country until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents or Program Patents Covering such Product in the country in which such Product is made, used or sold, [***] (such royalty period, the "***Royalty Period***").

(b) **Royalty Reduction – U.S. Loss of Patent Rights.** If (i) there is no longer a Valid Claim within the Licensed Patents or Program Patents Covering a Product in the U.S., and [***], then JBI may reduce the royalty payments for sales in the U.S. described in Table 4 by [***] ([***]) percent. JBI shall make the reduced royalty payments to Isis for the remainder of the Royalty Period.

(c) **Royalty Reduction – Early Generic Product Entry.** If after the [***] anniversary of the First Commercial Sale of a Product, in a given country within the Territory, entry of a Generic Product has occurred prior to the expiry of the last Licensed Patent or Program Patent with a Valid Claim covering a Product, and either (i) subsequently the sales of the Product have declined by [***] percent ([***]%) or more but less than [***] percent ([***]%) as compared to the [***] Calendar Quarters [***] prior to such Generic Product entry, then JBI may reduce the royalty payments for sales in such country described in Table 4 by [***] percent ([***]%), or (ii) subsequently the sales of the Product have declined by [***] percent ([***]%) or more as compared to the [***] Calendar Quarters [***] prior to such Generic Product entry, then no further royalty payments shall be due to Isis for such Product in such country; provided, if JBI reduced or ceased paying the royalty payments under this Section, and thereafter a court of competent jurisdiction determines that the Licensed Patent is valid and infringed by the Generic Product, JBI shall resume making royalty payments at the full amount as of the date of such court order.

(d) **Limitation on Aggregate Reduction for JBI Royalties**.

(i) In no event will the aggregate royalty offsets under Section 6.9.3(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to [***]% of the JBI Royalty rates listed in TABLE 4.

(ii) In addition, in no event will the aggregate royalty offsets and reductions under Section 6.8.2(c) (as applicable) and Section 6.9.3(b) reduce the royalties payable to Isis on Net Sales of a Product in any given period to less than [***].

(e) **End of Royalty Obligation**. On a country-by-country and Product-by-Product basis JBI's obligation to make royalty payments hereunder for such Product in such country will end on the expiration of the Royalty Period at which time JBI will have a fully paid up license under the Licensed Patents; provided [***].

6.9 **Third Party Payment Obligations**.

6.9.1 **Existing Isis In-License Agreements**.

(a) Certain of the Licensed Technology Controlled by Isis as of the Effective Date licensed to JBI under Section 4.1.1 was in-licensed or was acquired by Isis under the agreements with Third Party licensors or sellers listed on SCHEDULE 6.9.1 (all such license or purchase agreements being the "***Isis In-License Agreements***"). Certain license fees, maintenance fees, milestone payments, royalties or similar payments that apply to Products may become payable by Isis to such Third Parties under the Isis In-License Agreements based on the Development and Commercialization of a Product by JBI under this Agreement.

(b) Any payment obligations arising under the Isis In-License Agreements as existing on the Effective Date and up until JBI exercises an Option under this Agreement, as they apply to the Isis Core Technology used by Products developed under this Agreement will be paid by [***], and [***], as [***]. In the event JBI determines that it wishes to obtain a sublicense under the Isis In-License Agreements, [***].

6.9.2 **New In-Licensed Isis Product-Specific Patents**. If after the Effective Date, Isis obtains Third Party Patent Rights necessary or useful to Develop, Manufacture or Commercialize a Product that would have been considered an Isis Product-Specific Patent had Isis Controlled such Patent Rights on the Effective Date, to the extent Controlled by Isis, Isis will include such Third Party Patent Rights in the license granted to JBI under Section 4.1.1 if JBI agrees in writing to pay Isis (i) [***] and (ii) [***]. In the event JBI declines to pay Isis [***], nothing in this Agreement [***].

6.9.3 **Additional Core IP In-License Agreements**.

(a) JBI will promptly provide Isis written notice of any Additional Core IP JBI believes it has identified and Isis will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Core IP. If Isis obtains such a Third Party license, Isis will include such Additional Core IP in the license granted to JBI under Section 4.1.1, and any financial obligations under such Third Party agreement will be [***].

(b) If, however, Isis elects not to obtain such a license to such Third Party intellectual property, Isis will so notify JBI, and JBI may obtain such a Third Party license and, subject to Section 6.8.2(d), JBI may offset an amount equal to [***]% of any [***] paid by JBI under such Third Party license against any [***] of this Agreement in such country for [***].

(c) If it is unclear whether certain intellectual property identified by JBI pursuant to Section 6.9.3(a) is Additional Core IP under Section 6.9.3(b), Isis will send written notice to such effect to JBI, and the Parties will engage a mutually agreed upon independent Third Party intellectual property lawyer with expertise in the patenting of ASOs, and appropriate professional credentials in the relevant jurisdiction, to determine the question of whether or not such Third Party intellectual property is Additional Core IP. The determination of the Third Party expert engaged under the preceding sentence will be binding on the Parties solely for purposes of determining whether JBI is permitted to [***]. The costs of any Third Party expert engaged under this Section 6.9.3(c) will be paid by the Party against whose position the Third Party lawyer's determination is made.

6.9.4 **Other Third Party Payments**.

(a) **Isis' Third Party Agreements**. Except as otherwise expressly agreed to by JBI under Section 6.9.2, after Option exercise, JBI will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Isis.

(b) **JBI's Third Party Agreements**. Without limiting any applicable [***] under Section 6.9.3(b), JBI will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by JBI as they apply to Products.

6.10 **Invoices.** Unless otherwise specified hereunder, JBI shall make payments required hereunder to Isis within [***] ([***]) days from the date an invoice is received by JBI provided that any invoiced costs are for fees or services that have been rendered by Isis plus Out of Pocket Expenses incurred by Isis and further subject to the invoice having been received by JBI. All invoices must reference a valid Purchase Order (PO) Number which JBI shall provide to Isis within [***] ([***]) days of any such contracted service after the Effective Date. Isis' invoices will include Isis' good faith estimate of the FTE cost incurred by Isis in performing the services and the amount of Out-of Pocket Expenses incurred and charged by Isis. Before Isis commences work, JBI and Isis will agree to a budget for the work JBI requests Isis to perform that will include Isis' good faith estimate of the FTE cost plus Out of Pocket Expenses. Isis shall provide reasonable support for each invoice. Reasonable support means [***]. Invoices shall be sent to: Johnson & Johnson Shared Services, P.O. Box 16540, New Brunswick, NJ 08906-6540, United States, with a copy to Immunology TA Controller, c/o J&J PRD, PO Box 766, Welsh & McKean Road, Spring House 19477, or via www.ap.jnj.com if Isis is established with a web invoice account. JBI reserves the right to return to Isis unprocessed and unpaid those invoices that do not reference a valid P.O. number.

6.11 **Payments**.

6.11.1 **Commencement**. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, JBI will make royalty payments to Isis under this Agreement within [***] days following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report showing on a Product-by Product and country-by-country basis the gross sales, the Net Sales, and a calculation of the amount of royalty due on such Net Sales. This report shall also include the exchange rates and other methodology used in converting Net Sales into US dollars from the currencies in which sales were made in order to determine the appropriate royalty tier and royalty. If no royalties are payable in respect of a given Calendar Quarter, JBI will submit a written royalty report to Isis so indicating together with an explanation as to why no such royalties are payable. In addition, on a Product-by-Product basis, beginning with the Calendar Quarter in which the First Commercial Sale for such Product is made and for each Calendar Quarter thereafter for the next [***] ([***]) years, JBI will (based on information JBI collects, and in a format JBI uses for its own internal planning and reporting purposes) provide Isis a preliminary non-binding report estimating the total Net Sales of, and royalties payable to Isis for Products projected for such Calendar Quarter. JBI will endeavor to provide such preliminary non-binding report within [***] Business Days following the end of each such Calendar Quarter; provided JBI will provide such preliminary non-binding report no later than [***] Business Days following the end of each such Calendar Quarter.

6.11.2 **Mode of Payment**. All payments under this Agreement will be (i) payable in full in U.S. dollars, regardless of the country(ies) in which sales are made, (ii) made by wire transfer of immediately available funds to an account designated by Isis in writing, and (iii) non-creditable, irrevocable and non-refundable. With respect to sales of Product invoiced in a currency other than USD, such amounts and the amounts payable hereunder shall be expressed in their USD equivalent calculated as follows: For the upcoming Calendar Year, JBI shall provide: 1) a Currency Hedge Rate(s) to be used for the local currency of each country of the Territory and 2) the details of such Currency Hedge Rate(s) in writing to Isis not later than [***] business days after the Currency Hedge Rate(s) are available from the GTSC or its Affiliates, which is customarily at the end of October. Such Currency Hedge Rate(s) will remain constant throughout the upcoming calendar year. JBI shall use the Currency Hedge Rate(s) to convert Net Sales to USD for the purpose of calculating royalties and Sales Milestones.

6.11.3 **Records Retention**. Commencing with the First Commercial Sale of a Product, JBI will keep complete and accurate records pertaining to the sale of Products for a period of [***] Calendar Years after the year in which such sales occurred, and in sufficient detail to permit Isis to confirm the accuracy of the Net Sales or royalties paid by JBI hereunder.

6.12 **Audits**. After Option exercise, during the Agreement Term and for a period of [***] Calendar Years thereafter, at the written request and expense of Isis, JBI will permit an independent certified public accountant of nationally recognized standing appointed by Isis and reasonably acceptable to JBI, at reasonable times and upon reasonable notice, but in no case more than [***], to examine such records at the location where such records are maintained as may be necessary for the sole purpose of verifying the calculation and reporting of milestones and Net Sales, and the correctness of any milestone and royalty payments made under this Agreement for any period within the preceding [***] Calendar Years. As a condition to examining any records of JBI, such auditor will sign a nondisclosure agreement reasonably acceptable to JBI in form and substance. Any and all records of JBI examined by such independent certified public accountant will be deemed JBI's Confidential Information. The report of the independent public accountant shall be shared with JBI prior to distribution to Isis such that JBI can provide the independent public accountant with justifying remarks for inclusion in the report prior to sharing the conclusions of such independent public audit with Isis. Upon completion of the audit, the accounting firm will provide both JBI and Isis with a written report disclosing whether the royalty payments made by JBI are correct or incorrect, whether any milestone payment that became due during the audited period was timely reported and paid, and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of JBI, it is shown that JBI's royalty payments under this Agreement were less than the royalty amount which should have been paid, and/or that any milestone payment was not paid when due or at all, then JBI will make all payments required to be made by paying Isis the difference between such amounts to eliminate any discrepancy revealed by said inspection within [***] days of receiving the Audit Report, with interest calculated in accordance with Section 6.14. If, as a result of any inspection of the books and records of JBI, it is shown that JBI's payments under this Agreement were greater than the royalty amount which should have been paid, then JBI will receive a credit against future royalty payments due under Section 6.8 equal to the difference between the amounts paid by JBI and the royalty amounts which should have been paid. Isis will pay for such audit, except that if JBI is found to have underpaid Isis by more than [***]% of the amount that should have been paid, and/or not to have paid any milestone that should have been paid, JBI will reimburse Isis' reasonable costs of the audit.

6.13 Taxes.

6.13.1 **Taxes on Income**. Each Party will be solely responsible for the payment of all taxes imposed on its share of income arising directly or indirectly from the activities of the Parties under this Agreement.

6.13.2 Isis will provide JBI with any and all tax forms in advance of the due dates that may be reasonably necessary in order for JBI to lawfully not withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Following JBI's timely receipt of such tax forms from Isis, JBI will not withhold tax or will withhold tax at a reduced rate under an applicable bilateral income tax treaty, if appropriate under the applicable laws. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by applicable law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 6.13.2.

6.13.3 JBI will make all payments to Isis under this Agreement without deduction or withholding for Taxes except to the extent that any such deduction or withholding is required by law in effect at the time of payment.

6.13.4 Any Tax required to be withheld on amounts payable under this Agreement will be paid by JBI on behalf of Isis to the appropriate governmental authority, and JBI will furnish Isis with proof of payment of such Tax. Any such Tax required to be withheld will be an expense of and borne by Isis. If any such Tax is assessed against and paid by JBI, then Isis will indemnify and hold harmless JBI from and against such Tax unless the assessment and payment of such Tax is a result of acts or omissions by JBI.

6.13.5 JBI and Isis will cooperate with one another and use reasonable efforts to lawfully avoid or reduce withholding or similar obligations in respect of royalties, milestone payments and other payments made by the paying Party to the receiving party under this agreement, including but not limited to all documentation required by any taxing authority or reasonably requested by either Party to secure a reduction in the rate of applicable withholding Taxes or similar obligations. Within five Business Days of the Effective Date of this Agreement, Isis will deliver to JBI an accurate and complete Internal Revenue Service Form W-9.

6.13.6 The provisions of this Section 6.13 Are to be read in conjunction with the provisions of Section 12.4 below.

6.14 **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest at a rate per annum equal to the lesser of (i) the rate announced by Bank of America (or its successor) as its prime rate in effect on the date that such payment would have been first due plus 1% or (ii) the maximum rate permissible under applicable law.

6.15 **Paying Agent.** Janssen Research & Development, L.L.C., an Affiliate of JBI acting as a paying agent for JBI, may make certain payments due under this Agreement.

ARTICLE 7.
INTELLECTUAL PROPERTY

7.1 **Ownership**.

7.1.1 **Isis Technology and JBI Technology**. As between the Parties, Isis will own and retain all of its rights, title and interest in and to the Licensed Know-How and Licensed Patents and JBI will own and retain all of its rights, title and interest in and to the JBI Know-How and JBI Patents, subject to any assignments, rights or licenses expressly granted by one Party to the other Party under this Agreement.

7.1.2 **Agreement Technology**. As between the Parties, JBI is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of JBI or its Affiliates during the Drug Discovery Term ("***JBI Program Know-How***") and any Patent Rights that claim or cover JBI Program Know-How ("***JBI Program Patents***" and together with the JBI Program Know-How, the "***JBI Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by JBI to Isis under this Agreement. As between the Parties, Isis is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Isis or its Affiliates during the Drug Discovery Term ("***Isis Program Know-How***") and any Patent Rights that claim or cover such Know-How ("***Isis Program Patents***" and together with the Isis Program Know-How, the "***Isis Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any assignment, rights or licenses expressly granted by Isis to JBI under this Agreement. Any Know-How discovered, developed, invented or created jointly during the Drug Discovery Term by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf ("***Jointly-Owned Program Know-How***"), and any Patent Rights that claim or cover such Jointly-Owned Program Know-How ("***Jointly-Owned Program Patents***", and together with the Jointly-Owned Program Know-How, the "***Jointly-Owned Program Technology***"), are owned jointly by JBI and Isis on an equal and undivided basis, including all rights, title and interest thereto, subject to any rights or licenses expressly granted by one Party to the other Party under this Agreement. Except as expressly provided in this Agreement, neither Party will have any obligation to account to the other for profits with respect to, or to obtain any consent of the other Party to license or exploit, Jointly-Owned Program Technology by reason of joint ownership thereof, and each Party hereby waives any right it may have under the laws of any jurisdiction to require any such consent or accounting. Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, development, invention or creation of any Jointly-Owned Program Technology. The JBI Program Patents, Isis Program Patents and Jointly-Owned Program Patents are collectively referred to herein as the "***Program Patents***."

7.1.3 Joint Patent Committee.

(a) The Parties will establish a "***Joint Patent Committee***" or "***JPC***." The JPC will serve as the primary contact and forum for discussion between the Parties with respect to intellectual property matters arising under this Agreement, and will cooperate with respect to the activities set forth in this 7.1.3. Isis' obligation to participate in the JPC will terminate upon the end of the Drug Discovery Term. Thereafter, Isis will have the right, but not the obligation, to participate in JPC meetings. If the JPC dissolves, each Party will designate a patent attorney who will be responsible for intellectual property matters under this Agreement. A strategy will be discussed with regard to (i) prosecution and maintenance, defense and enforcement of Isis Product-Specific Patents that would be or are licensed to JBI under Section 4.1.1 in connection with a Product and JBI Product-Specific Patents, (ii) defense against allegations of infringement of Third Party Patent Rights, (iii) licenses to Third Party Patent Rights or Know-How, and (iv) the timing and subject matter of any potential publications regarding a Drug Discovery Program, in each case to the extent such matter would be reasonably likely to have a material impact on the Agreement or the licenses granted hereunder, which strategy will be considered in good faith by the Party entitled to prosecute, enforce and defend such Patent Rights, as applicable, hereunder, but will not be binding on such Party.

(b) In addition, the Joint Patent Committee will be responsible for the determination of inventorship of Program Patents in accordance with United States patent laws. In case of a dispute in the Joint Patent Committee (or otherwise between Isis and JBI) over inventorship of Program Patents, if the Joint Patent Committee cannot resolve such dispute, even after seeking the JRC's input, such dispute will be resolved by independent patent counsel not engaged or regularly employed in the past two years by either Party and reasonably acceptable to both Parties. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be shared equally by the Parties.

(c) The JPC will comprise an equal number of members from each Party. The Joint Patent Committee will meet as often as agreed by them (and at least semi-Annually), to discuss matters arising out of the activities set forth in this 7.1.3. The JPC will determine the JPC operating procedures at its first meeting, including the JPC's policies for replacement of JPC members, and the location of meetings, which will be codified in the written minutes of the first JPC meeting. To the extent reasonably requested by either Party, the Joint Patent Committee will solicit the involvement of more senior members of their respective legal departments (up to the most senior intellectual property attorney, where appropriate) with respect to critical issues, and may escalate issues to the Executives for input and resolution pursuant to Section 12.1. Each Party's representatives on the Joint Patent Committee will consider comments and suggestions made by the other in good faith. If either Party deems it reasonably advisable, the Parties will enter into a mutually agreeable common interest agreement covering the matters contemplated by this Agreement. Each party shall bear their own cost of participation on the JPC.

7.2 Prosecution and Maintenance of Patents.

7.2.1 Patent Filings. The Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Section 7.2.2 and Section 7.2.3 will endeavor to obtain patent protection for the applicable Product as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice but reasonably acceptable to the other Party, in such countries as the responsible Party sees fit.

7.2.2 Licensed Patents and JBI Patents.

(a) **Licensed Patents In General**. Prior to exercise of an Option, Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Licensed Patents that are the subject of such Option, subject to Section 7.2.2(b), Section 7.2.3 and Section 7.2.4. During the Agreement Term, Isis will control and be responsible for all aspects of the Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, and Isis Formulation Patents.

(b) **Licensed Patents After Option Exercise**. After JBI exercises its Option for a particular Drug Discovery Program, JBI will control and be responsible for all aspects of the Prosecution and Maintenance of all Isis Product-Specific Patents and Jointly-Owned Program Patents that cover Products under such Research project to the same extent Isis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such Option exercise, subject to Section 7.2.3 and Section 7.2.4, and will grant Isis the license set forth in Section 4.2.2.

(c) **JBI Patents**. JBI will control and be responsible for all aspects of the Prosecution and Maintenance of all JBI Patents, subject to Section 7.2.3 and Section 7.2.4.

7.2.3 **Jointly-Owned Program Patents**. Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that are not Product Specific Patents. Prior to exercise of an Option, Isis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that are Product Specific Patents and the subject of such Option. After exercise of an Option, JBI will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that are Product Specific Patents and are the subject of such exercised Option.

7.2.4 **Other Matters Pertaining to Prosecution and Maintenance of Patents**.

(a) Each Party will keep the other Party informed through the Joint Patent Committee as to material developments with respect to the Prosecution and Maintenance of the Product-Specific Patents or Jointly-Owned Program Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 7.2.2, Section 7.2.3 or this Section 7.2.4, including by providing copies of material data as it arises, any office actions or office action responses or other correspondence that such Party provides to or receives from any patent office, including notice of all interferences, reissues, re-examinations, oppositions or requests for patent term extensions, and all patent-related filings, and by providing the other Party the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance.

(b) If JBI elects (a) not to file and prosecute patent applications for the Jointly-Owned Program Patent Rights or Isis Product-Specific Patents that have been licensed or assigned to JBI under this Agreement or the JBI Product-Specific Patents ("***JBI-Prosecuted Patents***") in a particular country, (b) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) or maintenance of any JBI-Prosecuted Patent in a particular country, or (c) not to file and prosecute patent applications for the JBI-Prosecuted Patent in a particular country following a written request from Isis to file and prosecute in such country, then JBI will so notify Isis promptly in writing of its intention (including a reasonably detailed rationale for doing so) in good time to enable Isis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and Isis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such JBI-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, JBI will cooperate with Isis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such JBI-Prosecuted Patent in such country in Isis' own name, but only to the extent that JBI is not required to take any position with respect to such abandoned JBI-Prosecuted Patent that would be reasonably likely to adversely affect the scope, validity or enforceability of any of the other Patent Rights being prosecuted and maintained by JBI under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Isis assumes responsibility for the Prosecution and Maintenance of any such JBI-Prosecuted Patent under this Section 7.2.4(b), Isis will have no obligation to notify JBI if Isis intends to abandon such JBI-Prosecuted Patent.

(c) If, during the Agreement Term, Isis intends to abandon any Isis Product-Specific Patent for which Isis is responsible for Prosecution and Maintenance without first filing a continuation or substitution, then, if the applicable Option Deadline has not passed, Isis will notify JBI of such intention at least 60 days before such Patent Right will become abandoned, and JBI will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 7.3.1) with counsel of its own choice. Notwithstanding anything to the contrary in this Agreement, if JBI assumes responsibility for the Prosecution and Maintenance of any such Isis Product-Specific Patent under this Section 7.2.4(c), JBI will have no obligation to notify Isis if JBI intends to abandon such Isis Product-Specific Patent.

(d) The Parties, through the Joint Patent Committee, will cooperate in good faith to determine if and when any divisional or continuation applications will be filed with respect to any Program Patents or Product-Specific Patents, and where a divisional or continuation patent application filing would be practical and reasonable, then such a divisional or continuation filing will be made.

(e) If the Party responsible for Prosecution and Maintenance pursuant to Section 7.2.3 intends to abandon such Jointly-Owned Program Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least 60 days before such Jointly-Owned Program Patent will become abandoned, and such other Party will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense (subject to Section 7.3.1) with counsel of its own choice, in which case the abandoning Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, title and interest in and to such Jointly-Owned Program Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Program Patents under this Section 7.2.4(e), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Program Patents.

(f) In addition, the Parties will consult, through the Joint Patent Committee, and take into consideration the comments of the other Party for all matters relating to interferences, reissues, re-examinations and oppositions with respect to those Patent Rights in which such other Party (i) has an ownership interest, (ii) has received a license thereunder in accordance with this Agreement, or (iii) may in the future, in accordance with this Agreement, obtain a license or sublicense thereunder.

7.3 Patent Costs.

7.3.1 Jointly-Owned Program Patents. Unless the Parties agree otherwise, Isis and JBI will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Program Patents; *provided that*, either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Program Patents in a particular country or particular countries, in which case the declining Party will, and will cause its Affiliates to, assign to the other Party (or, if such assignment is not possible, grant a fully-paid exclusive license in) all of their rights, titles and interests in and to such Jointly-Owned Program Patents.

7.3.2 Licensed Patents and JBI Patents. Except as set forth in Section 7.2.4 and Section 7.3.1, each Party will be responsible for all Patent Costs incurred by such Party prior to and after the Effective Date in all countries in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Section 7.2; *provided, however*, that after Option exercise, JBI will be solely responsible for Patent Costs arising from the Prosecution and Maintenance of the Isis Product-Specific Patents.

7.4 Defense of Claims Brought by Third Parties.

7.4.1 If a Third Party initiates a Proceeding claiming a Patent Right owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Product, (a) Isis will have the first right, but not the obligation, to defend against any such Proceeding initiated prior to Option exercise at its sole cost and expense and (b) JBI will have the first right, but not the obligation, to defend against any such Proceeding initiated after Option exercise at its sole cost and expense. If the Party having the first right to defend against such Proceeding (the "***Lead Party***") elects to defend against such Proceeding, then the Lead Party will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of the other Party, not to be unreasonably withheld, conditioned or delayed). The other Party will reasonably assist the Lead Party in defending such Proceeding and cooperate in any such litigation at the request and expense of the Lead Party. The Lead Party will provide the other Party with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 7.4, and the Lead Party will keep the other Party apprised of the progress of such Proceeding. If the Lead Party elects not to defend against a Proceeding, then the Lead Party will so notify the other Party in writing within 60 days after the Lead Party first receives written notice of the initiation of such Proceeding, and the other Party (the "***Step-In Party***") will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter the Step-In Party will have the sole right to direct the defense thereof, including the right to settle such claim. In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 7.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 7.4, and such Party will promptly furnish the other Party with a copy of each communication relating to the alleged infringement that is received by such Party.

7.4.2 **Discontinued Product**. If a Third Party initiates a Proceeding claiming that any Patent Right or Know-How owned by or licensed to such Third Party is infringed by the Development, Manufacture or Commercialization of a Discontinued Product, Isis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. JBI will reasonably assist Isis in defending such Proceeding and cooperate in any such litigation at the request and expense of Isis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Isis will provide JBI with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Isis becomes aware and that is of the type described in this Section 7.4.2, and Isis will promptly furnish JBI with a copy of each communication relating to the alleged infringement received by Isis.

7.4.3 **Interplay Between Enforcement of IP and Defense of Third Party Claims**. Notwithstanding the provisions of Section 7.4.1 and Section 7.4.2, to the extent that a Party's defense against a Third Party claim of infringement under this Section 7.4 involves (i) the enforcement of the other Party's Know-How or Patent Rights, or (ii) the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, then, in each case, the general concepts of Section 7.5 will apply to the enforcement of such other Party's Know-How or Patent Rights or the defense of such invalidity claim (*i.e.*, each Party has the right to enforce its own intellectual property, except that the relevant Commercializing Party will have the initial right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim, and the other Party will have a step-in right, to the extent provided in Section 7.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

7.5 **Enforcement of Patents Against Competitive Infringement**.

7.5.1 **Duty to Notify of Competitive Infringement**. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party to which such Party does not owe any obligation of confidentiality with respect to any Product-Specific Patents by reason of the development, manufacture, use or commercialization of a product directed against the RNA that encodes a Collaboration Target in the Field ("***Competitive Infringement***"), such Party will promptly notify the other Party in writing and will provide such other Party with available evidence of such Competitive Infringement; *provided*, *however*, that for cases of Competitive Infringement under Section 7.5.7 below, such written notice will be given within 10 days.

7.5.2 **Prior to Option Exercise**. For any Competitive Infringement with respect to a Product occurring after the Effective Date but before Option exercise, Isis will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding with respect thereto, by counsel of its own choice, and JBI will have the right to be represented in that action by counsel of its own choice at its own expense, *however*, Isis will have the sole right to control such litigation. Isis will provide JBI with prompt written notice of the commencement of any such Proceeding, and Isis will keep JBI apprised of the progress of such Proceeding. If Isis fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90 day extension to conclude negotiations, which extension will apply only in the event that Isis has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), JBI will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice; *provided that* Isis will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Isis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.2 to the extent involving any the Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, or Isis Formulation Patents.

7.5.3 **Following Option Exercise**. For any Competitive Infringement with respect to a particular Product (except for a Discontinued Product) occurring after Option exercise, so long as part of such Proceeding JBI also enforces any Patent Rights Controlled by JBI being infringed that Cover the Product, then JBI will have the first right, but not the obligation, to institute, prosecute, and control a Proceeding to enforce the Isis Product Specific Patents with respect thereto by counsel of its own choice at its own expense, and Isis will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however*, JBI will have the right to control such litigation. If JBI fails to initiate a Proceeding within a period of 90 days after receipt of written notice of such Competitive Infringement (subject to a 90-day extension to conclude negotiations, if JBI has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Isis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and JBI will have the right to be represented in any such action by counsel of its own choice at its own expense. Isis will at all times have the sole right to institute, prosecute, and control any Proceeding under this Section 7.5.3 to the extent involving any Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, or Isis Formulation Patents.

7.5.4 **Joinder**.

(a) If a Party initiates a Proceeding in accordance with this Section 7.5, the other Party agrees to be joined as a party plaintiff where necessary and to give the first Party reasonable assistance and authority to file and prosecute the Proceeding. Subject to Section 7.5.5, the costs and expenses of each Party incurred pursuant to this Section 7.5.4(a) will be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 7.5.4, the other Party may join such Proceeding as a party plaintiff where necessary for such other Party to seek lost profits with respect to such infringement.

7.5.5 **Share of Recoveries**. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.5 will be shared as follows:

(a) the amount of such recovery will first be applied to the Parties' reasonable Out-of-Pocket Costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); then

(b) any remaining proceeds constituting direct or actual damages for acts of infringement occurring prior to JBI's exercise of the Option will be (i) [***]; or (ii) [***]; then

(c) any remaining proceeds constituting direct or actual damages for acts of infringement occurring after JBI's exercise of the Option [***]; then

(d) any remaining proceeds constituting punitive or treble damages will be allocated between the Parties as follows: the Party initiating the Proceeding will receive and retain [***]% of such proceeds and the other Party will receive and retain [***]% of such proceeds.

7.5.6 **Settlement**. Notwithstanding anything to the contrary under this Section 7.5.6 neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this 7.5.6 that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license, covenant not to sue or similar immunity under a Patent Right Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent Right.

7.5.7 **35 USC 271(e)(2) Infringement**. Notwithstanding anything to the contrary in this Section 7.5, solely with respect to Licensed Patents that have not been assigned to JBI under this Agreement for a Competitive Infringement under 35 USC 271(e)(2), the time period set forth in Section 7.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of 25 days, so that, to the extent the other Party has the right, pursuant to such Section to initiate a Proceeding if the first Party does not initiate a Proceeding, such other Party will have such right if the first Party does not initiate a Proceeding within 25 days after such first Party's receipt of written notice of such Competitive Infringement.

7.6 **Other Infringement**.

7.6.1 **Jointly-Owned Program Patents**. With respect to the infringement of a Jointly-Owned Program Patent which is not a Competitive Infringement, the Parties will cooperate in good faith to bring suit together against such infringing party or the Parties may decide to permit one Party to solely bring suit. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 7.6.1 will be shared as follows: (i) the amount of such recovery will first be applied to the Parties' reasonable Out-of-Pocket costs incurred in connection with such Proceeding (which amounts will be allocated *pro rata* if insufficient to cover the totality of such expenses); (ii) any remaining proceeds constituting direct damages will be [***], and (iii) any remaining proceeds constituting punitive or treble damages will be allocated as follows: (A) if the Parties jointly initiate a Proceeding pursuant to this Section 7.6.1, each Party will receive [***]% of such proceeds; and (B) if only one Party initiates the Proceeding pursuant to this Section 7.6.1, such Party will receive [***]% of such proceeds and the other Party will receive [***]% of such proceeds.

7.6.2 **Patents Solely Owned by Isis**. Isis will retain all rights to pursue an infringement of any Patent Right solely owned by Isis which is other than a Competitive Infringement and Isis will retain all recoveries with respect thereto.

7.6.3 **Patents Solely Owned by JBI**. JBI will retain all rights to pursue an infringement of any Patent Right solely owned by JBI which is other than a Competitive Infringement and JBI will retain all recoveries with respect thereto.

7.7 **Patent Listing**. JBI will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and JBI will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the Joint Patent Committee for any such listing. Notwithstanding the preceding sentence, JBI will retain final decision-making authority as to the listing of all applicable Patent Rights for the Product that are not Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, or Isis Formulation Patents, regardless of which Party owns such Patent Rights.

7.8 **Joint research agreement under the Leahy-Smith America Invents Act.** In the event that a Party intends to so invoke the Leahy-Smith America Invents Act, once agreed to by the other Party, it will notify the other Party and the Parties shall use reasonable efforts to cooperate and coordinate their activities with such Party with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "joint research agreement" as defined in 35 U.S.C. § 100(h)

7.9 **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Technology under this Section 7.9 will be subject to the Third Party rights and obligations under any (i) New Third Party License the restrictions and obligations of which JBI has agreed to under Section 6.9.2, (ii) Prior Agreements, and (iii) Isis In-License Agreements; *provided*, *however*, that, to the extent that Isis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to JBI hereunder and, this Agreement purports to grant any such rights to JBI, Isis will act in such regard with respect to such Patent Rights at JBI's direction.

7.10 **Additional Right and Exceptions**. Notwithstanding any provision of this Section 7.10, Isis retains the sole right to Prosecute and Maintain Isis Core Technology Patents and Isis Manufacturing and Analytical Patents during the Agreement Term and to control any enforcement of Isis Core Technology Patents and Isis Manufacturing and Analytical Patents, and will take the lead on such enforcement solely to the extent that the scope or validity of any Patent Rights Controlled by Isis and Covering the Isis Core Technology Patents or Isis Manufacturing and Analytical Patents is at risk.

7.11 **Patent Term Extension.** The Parties will cooperate with each other in gaining patent term extension wherever applicable to the Product. After exercising an Option, JBI will determine which relevant patents will be extended.

7.12 **Rights in Bankruptcy.** All rights and licenses granted under or pursuant to any section of this Agreement are and will otherwise be deemed to be for purposes of Section 365(n) of Title 11, United States Code (the "Bankruptcy Code") licenses of rights to "intellectual property" as defined in Section 101(56) of the Bankruptcy Code. The Parties will retain and may fully exercise all of their respective rights and elections under the Bankruptcy Code. Upon the bankruptcy of any Party, the non-bankrupt Party will further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and such, if not already in its possession, will be promptly delivered to the non-bankrupt Party, unless the bankrupt Party elects in writing to continue, and continues, to perform all of its obligations under this Agreement.

ARTICLE 8.
REPRESENTATIONS AND WARRANTIES

8.1 **Representations and Warranties of Both Parties**. Each Party hereby represents and warrants to the other Party, as of the Effective Date, that:

8.1.1 such Party is duly organized, validly existing and in good standing under the laws of the jurisdiction of its incorporation or organization and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

8.1.2 such Party has taken all necessary action on its part to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

8.1.3 this Agreement has been duly executed and delivered on behalf of such Party, and constitutes a legal, valid and binding obligation, enforceable against it in accordance with the terms hereof;

8.1.4 the execution, delivery and performance of this Agreement by such Party will not constitute a default under or conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it is bound, or violate any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over such Party;

8.1.5 no government authorization, consent, approval, license, exemption of or filing or registration with any court or governmental department, commission, board, bureau, agency or instrumentality, domestic or foreign, under any applicable laws, rules or regulations currently in effect, is or will be necessary for, or in connection with, the transaction contemplated by this Agreement or any other agreement or instrument executed in connection herewith, or for the performance by it of its obligations under this Agreement and such other agreements; and

8.1.6 it has not employed (and, to the best of its knowledge, has not used a contractor or consultant that has employed) and in the future will not employ (or, to the best of its knowledge, use any contractor or consultant that employs, provided that such Party may reasonably rely on a representation made by such contractor or consultant) any Person debarred by the FDA (or subject to a similar sanction of EMA or foreign equivalent), or any Person which is the subject of an FDA debarment investigation or proceeding (or similar proceeding of EMA or foreign equivalent), in the conduct of the Pre-Clinical Studies or Clinical Studies of the Product and its activities under each Drug Discovery Program.

8.2 **Representations and Warranties of Isis**. Isis hereby represents and warrants to JBI, as of the Effective Date, that:

8.2.1 To the best of its knowledge and belief, there are no additional licenses (beyond those that would be granted to JBI under Section 4.1.1 upon the exercise of the Option for a Product arising under the Drug Discovery Programs) under any intellectual property owned or Controlled by Isis or its Affiliates as of the Effective Date that would be required in order for JBI to further Develop and Commercialize a Product.

8.2.2 Schedule 8.2.2(a), Schedule 8.2.2(b), Schedule 8.2.2(c) and Schedule 8.2.2(d) set forth true, correct and complete lists of all Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, and Isis Formulation Patents that apply to the Compounds contemplated under the Drug Discovery Programs as of the Effective Date (the ***"Isis Platform Technology"***), respectively, and indicates whether each such Patent Right is owned by Isis or licensed by Isis from a Third Party and if so, identifies the licensor or sublicensor from which the Patent Right is licensed. Isis Controls such Patent Rights existing as of the Effective Date and is entitled to grant all rights and licenses (or sublicenses, as the case may be) under such Patent Rights it purports to grant to JBI under this Agreement.

8.2.3 There are no claims, judgments or settlements against or owed by Isis or its Affiliates or pending against Isis or, to the best of Isis' knowledge, threatened against Isis, in each case relating to the Isis Platform Technology or Collaboration Targets that would prevent Isis from performing the activities under this Agreement or from granting JBI the licenses under Section 4.1. To the best of Isis' knowledge, there are no claims, judgments or settlements against or owed by any Third Party that is party to a Prior Agreement, or pending or threatened claims or litigation against any Third Party that is party to a Prior Agreement, in each case relating to the Isis Platform Technology or Collaboration Targets that would prevent Isis from performing the activities under this Agreement or from granting JBI the licenses under Section 4.1.

8.2.4 At the Effective Date (a) there is no fact or circumstance known by Isis that would cause Isis to reasonably conclude that any Isis Core Technology Patent or Isis Manufacturing and Analytical Patent is invalid or un-enforceable, (b) there is no fact or circumstance known by Isis that would cause Isis to reasonably conclude the inventorship of each Isis Core Technology Patent or Isis Manufacturing and Analytical Patent is not properly identified on each patent, and (c) all official fees, maintenance fees and annuities for the Isis Core Technology Patent or Isis Manufacturing and Analytical Patent have been paid.

8.2.5 All Isis In-License Agreements are in full force and effect and have not been modified or amended. Neither Isis nor, to the best knowledge of Isis, the Third Party licensor in an Isis In-License Agreement is in default with respect to a material obligation under such Isis In-License Agreement, and neither such party has claimed or has grounds upon which to claim that the other party is in default with respect to a material obligation under, any Isis In-License Agreement.

8.3 **Isis Covenants**. Isis hereby covenants to JBI that, except as expressly permitted under this Agreement:

8.3.1 Isis will promptly amend Schedule 8.2.2(a), Schedule 8.2.2(b) and Schedule 8.2.2(c) and submit such amended Schedules to JBI if Isis becomes aware that any Isis Core Technology Patents, Isis Manufacturing and Analytical Patents or Isis Product-Specific Patents are not properly identified on such Schedule.

8.3.2 During the Agreement Term, Isis will maintain and not breach any Isis In-License Agreements and any agreements with Third Parties entered into after the Effective Date ("***New Third Party Licenses***") that provide a grant of rights from such Third Party to Isis that are Controlled by Isis and are licensed or that Isis believes may become subject to a license from Isis to JBI for the Development Candidate under this Agreement;

8.3.3 Isis will promptly notify JBI of any material breach by Isis or a Third Party of any New Third Party License, and in the event of a breach by Isis, will permit JBI to cure such breach on Isis' behalf upon JBI's request;

8.3.4 Isis will not amend, modify or terminate any Isis In-License Agreement or New Third Party License in a manner that would adversely affect JBI's rights hereunder without first obtaining JBI's written consent, which consent may be withheld in JBI's sole discretion; and

8.3.5 all of Isis' employees performing activities hereunder on behalf of Isis will be obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to Isis as the sole owner thereof.

8.4 **DISCLAIMER. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY NOR ITS AFFILIATES MAKES ANY REPRESENTATION OR EXTENDS ANY WARRANTY OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. JBI AND ISIS UNDERSTAND THAT EACH PRODUCT IS THE SUBJECT OF ONGOING RESEARCH AND DEVELOPMENT AND THAT NEITHER PARTY CAN ASSURE THE SAFETY, USEFULNESS OR COMMERCIAL OR TECHNICAL VIABILITY OF EACH PRODUCT.**

ARTICLE 9.
INDEMNIFICATION; INSURANCE

9.1 **Indemnification by JBI**. JBI will indemnify, defend and hold harmless Isis and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all liabilities, damages, losses, costs and expenses including the reasonable fees of attorneys (collectively "***Losses***") arising out of or resulting from any and all Third Party suits, claims, actions, proceedings or demands ("***Claims***") based upon:

9.1.1 the gross negligence or willful misconduct of JBI, its Affiliates or Sublicensees and its or their respective directors, officers, employees and agents, in connection with JBI's performance of its obligations or exercise of its rights under this Agreement;

9.1.2 any breach of any representation or warranty or express covenant made by JBI under ARTICLE 8 or any other provision under this Agreement;

9.1.3 the Development or Manufacturing activities that are conducted by or on behalf of JBI or its Affiliates or Sublicensees; or

9.1.4 the Commercialization of a Product by or on behalf of JBI or its Affiliates or Sublicensees;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of Isis or its Affiliates, licensees, Sublicensees or contractors, and its or their respective directors, officers, employees and agents or other circumstance in each case for which Isis has an indemnity obligation pursuant to Section 9.2.

9.2 **Indemnification by Isis**. Isis will indemnify, defend and hold harmless JBI and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all Losses arising out of or resulting from any and all Claims based upon:

9.2.1 the gross negligence or willful misconduct of Isis, its Affiliates or Sublicensees or its or their respective directors, officers, employees and agents, in connection with Isis' performance of its obligations or exercise of its rights under this Agreement;

9.2.2 any breach of any representation or warranty or express covenant made by Isis under ARTICLE 8 or any other provision under this Agreement; or

9.2.3 any development, manufacturing or commercialization activities that are conducted by or on behalf of Isis or its Affiliates or Sublicensees with respect to a Discontinued Product.

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to any acts or omissions of JBI or its Affiliates, licensees, Sublicensees or contractors and its or their respective directors, officers, employees and agents or other circumstance, in each case for which JBI has an indemnity obligation pursuant to Section 9.1.

9.3 **Procedure**. If a Person entitled to indemnification under Section 9.1 or Section 9.2 (an "***Indemnitee***") seeks such indemnification, such Indemnitee will (i) inform the indemnifying Party in writing of a Claim as soon as reasonably practicable after such Indemnitee receives notice of such Claim, (ii) permit the indemnifying Party to assume direction and control of the defense of the Claim (including the sole right to settle such Claim at the sole discretion of the indemnifying Party, *provided that* (A) such settlement or compromise does not admit any fault or negligence on the part of the Indemnitee, or impose any obligation on, or otherwise materially adversely affect, the Indemnitee or other Party and (B) the indemnifying Party first obtain the written consent of the Indemnitee with respect to such settlement, which consent will not be unreasonably withheld), (iii) cooperate as reasonably requested (at the expense of the indemnifying Party) in the defense of the Claim, and (iv) undertake reasonable steps to mitigate any Losses with respect to the Claim. The provisions of Section 7.4 will govern the procedures for responding to a Claim of infringement described therein. Notwithstanding anything in this Agreement to the contrary, the indemnifying Party will have no liability under Section 9.1 or Section 9.2, as the case may be, for Claims settled or compromised by the Indemnitee without the indemnifying Party's prior written consent.

9.4 **Insurance**.

9.4.1 **Isis' Insurance Obligations**. Isis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement.

9.4.2 **JBI's Insurance Obligations**. JBI will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement, *provided, that*, at a minimum, JBI will maintain, in force from [***] days prior to enrollment of the first patient in a Clinical Study, a clinical trials/product liability insurance policy providing coverage of at least $[***] per claim and $[***] Annual aggregate and, *provided further* that such coverage is increased to at least $[***] at least [***] days before JBI initiates the First Commercial Sale of a Product hereunder. JBI will furnish to Isis evidence of such insurance upon request. Notwithstanding the foregoing, JBI may self-insure to the extent that it self-insures for its other products, but at a minimum will self-insure at levels that are consistent with levels customarily maintained against similar risks by similar companies in JBI's industry.

9.5 **LIMITATION OF CONSEQUENTIAL DAMAGES. EXCEPT FOR (a) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 9, (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT UNDER THIS AGREEMENT, (c) A PARTY'S BREACH OF ARTICLE 2, OR A BREACH OF SECTION 10.3.4(a) BY JBI OR ITS AFFILIATES OR (d) CLAIMS ARISING OUT OF A PARTY'S BREACH OF ITS CONFIDENTIALITY OBLIGATIONS UNDER THIS AGREEMENT, NEITHER PARTY NOR ANY OF ITS AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INCIDENTAL, CONSEQUENTIAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES OR LOST OR IMPUTED PROFITS OR ROYALTIES, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.**

ARTICLE 10.
TERM; TERMINATION

10.1 **Agreement Term; Expiration**. This Agreement is effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 10, will continue in full force and effect until the expiration of all payment obligations under this Agreement with respect to all Products in all countries; *provided, however,* that if every Option either (a) has expired as a result of JBI not providing Isis a written notice stating JBI is exercising such Option and paying Isis the applicable license fee under Section 6.4 by the applicable Option Deadline, or (b) has been terminated prior to Option exercise pursuant to Section 10.2.1 or 10.2.2, then this Agreement will expire on the expiration or termination, as applicable, of the last Option.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 10.1 is the "***Agreement Term***."

10.2 Termination of the Agreement.

10.2.1 JBI's Termination for Convenience. At any time following payment by JBI of the upfront fee under Section 6.1, subject to Section 10.3.1 below, JBI will be entitled to terminate this Agreement as a whole, or terminate this Agreement in part with respect to a particular Drug Discovery Program and applicable Collaboration Target, for convenience by providing 90 days written notice to Isis of such termination.

10.2.2 Termination for Material Breach.

(a) **JBI's Right to Terminate**. If JBI believes that Isis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 1.2.5, which is governed by Section 10.2.3 below), then JBI may deliver notice of such material breach to Isis. If the breach is curable, Isis will have 60 days to cure such breach. If Isis fails to cure such breach within the 60 day period, or if the breach is not subject to cure, JBI may terminate this Agreement as a whole, or terminate this Agreement in part with respect to the particular Program affected by such breach, and the applicable Collaboration Target, by providing written notice to Isis. Without limiting the foregoing, breach by a Party of ARTICLE 2 of this Agreement constitutes a material breach of this Agreement with respect to the Program affected by such breach and the applicable Collaboration Target.

(b) **Isis' Right to Terminate**. If Isis believes that JBI is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 1.2.5, Section 5.1 or Section 5.2, which is governed by Section 10.2.3 below), then Isis may deliver notice of such material breach to JBI. If the breach is curable, JBI will have 60 days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within 30 days following such notice). If JBI fails to cure such breach within the 60 day or 30 day period, as applicable, or if the breach is not subject to cure, Isis in its sole discretion may terminate this Agreement with respect to the Drug Discovery Program(s) and the applicable Collaboration Target(s) affected by such breach by providing written notice thereof to JBI. To the extent such material breach is uncured for one Drug Discovery Program, the remaining active Drug Discovery Programs for which there is no uncured material breach shall remain in effect.

10.2.3 **Remedies for Failure to Use Commercially Reasonable Efforts**.

(a) If Isis, in JBI's reasonable determination, fails to use Commercially Reasonable Efforts in the activities contemplated in Section 1.2.5 prior to Option exercise with respect to a particular Drug Discovery Program or with respect to other agreed-upon activities to be performed by Isis associated with the research, Development, or Commercialization of a Product, under this Agreement, JBI will notify Isis and, within 30 days thereafter, Isis and JBI will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to Isis' use of Commercially Reasonable Efforts in Section 1.2.5 or for activities otherwise agreed upon by Isis under this Agreement. Following such a meeting, if Isis fails to use Commercially Reasonable Efforts as contemplated by Section 1.2.5 with respect to such Drug Discovery Program, then subject to Section 10.2.4 below, JBI will have the right to terminate this Agreement as it relates to the applicable Drug Discovery Program.

(b) If JBI, in Isis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 1.2.5, Section 5.1 or Section 5.2 with respect to a Product or Drug Discovery Program above, Isis will notify JBI and, within 30 days thereafter, Isis and JBI will meet and confer to discuss and resolve the matter in good faith, and attempt to devise a mutually agreeable plan to address any outstanding issues related to JBI's use of Commercially Reasonable Efforts in Section 1.2.5, Section 5.1 or Section 5.2. Following such a meeting, if JBI fails to use Commercially Reasonable Efforts with respect to the applicable Product or Drug Discovery Program as contemplated by Section 1.2.5, Section 5.1 or Section 5.2, then subject to Section 10.2.4 below, Isis will have the right, at its sole discretion, to terminate this Agreement as it relates to such Product or Drug Discovery Program.

10.2.4 **Disputes Regarding Material Breach**. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.2 or Section 10.2.3 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such 60 day period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.2.2 or Section 10.2.3, as applicable, unless and until it has been determined in accordance with Section 12.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within 30 days following such determination. It is understood and acknowledged that during the pendency of such dispute, all the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder, including satisfying any payment obligations.

10.2.5 **Termination for Patent Challenge**. Isis may terminate this Agreement, if JBI disputes, [***] validity [***], provided however that, [***] Isis shall not have the right to terminate if [***]:

(a) JBI asserts invalidity as a defense in any court proceeding bought by Isis asserting infringement of a granted Patent within the Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, or [***]; or

(b) JBI (i) acquires a Third Party that has an existing challenge, whether in a court or administrative proceeding, against a granted Patent within the Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, or Isis Formulation Patents or (ii) licenses a product for which Isis has an existing challenge, whether in a court or administrative proceeding, against [***].

10.2.6 **Termination for Insolvency**. Either Party may terminate this Agreement if, at any time, the other Party files in any court or agency pursuant to any statute or regulation of any state or country a petition in bankruptcy or insolvency or for reorganization or for an arrangement or for the appointment of a receiver or trustee of the Party or of substantially all of its assets; or if the other Party proposes a written agreement of composition or extension of substantially all of its debts; or if the other Party will be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition will not be dismissed within 90 days after the filing thereof; or if the other Party will propose or be a party to any dissolution or liquidation; or if the other Party will make an assignment of substantially all of its assets for the benefit of creditors.

10.3 **Consequences of Expiration or Termination of the Agreement**.

10.3.1 **In General**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 at any time and for any reason, the following terms will apply to any Drug Discovery Program that is the subject of such expiration or termination:

(a) **Return of Information and Materials**. The Parties will return (or destroy, as directed by the other Party) all data, files, records and other materials containing or comprising the other Party's Confidential Information, except to the extent such Confidential Information is necessary or useful to conduct activities under a surviving Drug Discovery Program. Notwithstanding the foregoing, the Parties will be permitted to retain one copy of such data, files, records, and other materials for archival and legal compliance purposes.

(b) **Accrued Rights**. Termination or expiration of this Agreement for any reason will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination or expiration. Such termination or expiration will not relieve a Party from obligations that are expressly indicated to survive the termination or expiration of this Agreement. For purposes of clarification, milestone payments under ARTICLE 6 accrue as of the date the applicable Milestone Event is achieved even if the payment is not due at that time.

(c) **Survival**. The following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 4.1.2(c) (Effect of Termination on Sublicenses), Section 4.2.2, Section 6.11.3 (Records Retention), Section 6.12 (Audits), Section 7.1.1 (Isis Technology and JBI Technology), Section 7.1.2 (Agreement Technology), Section 8.4 (Disclaimer), ARTICLE 9 (Indemnification; Insurance), Section 10.2.5 (Termination for Insolvency), Section 10.3 (Consequences of Expiration or Termination of the Agreement), ARTICLE 11 (Confidentiality), ARTICLE 12 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

10.3.2 **Perpetual, Royalty-Free Non-Exclusive License**. If JBI has exercised its Option for a particular Drug Discovery Program, then upon expiration of the Royalty Period in all countries in which the applicable Products are being or have been sold, Isis will and hereby does grant to JBI a perpetual, nonexclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Isis Know-How to Manufacture, Develop and Commercialize any Product under such Drug Discovery Program.

10.3.3 **Termination Before Option Exercise**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 before Option exercise, then, in addition to the terms set forth in Section 10.3.1, the following terms will apply to each Drug Discovery Program that is the subject of such expiration or termination:

(a) JBI's Option under Section 3.1 will expire and Isis will be free to Develop and Commercialize Compounds included in such Drug Discovery Program on its own or with a Third Party.

(b) Neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the terminated Drug Discovery Program(s).

(c) To the extent requested by Isis, JBI will promptly transfer to Isis all data, results and information (including JBI's Confidential Information and any regulatory documentation (including drafts)) related to the terminated Drug Discovery Program(s) in the possession of JBI and its contractors to the extent such data, results and information were generated by or on behalf of JBI under this Agreement.

(d) Except as explicitly set forth in Section 10.3.1(a), Section 10.3.1(b) or Section 10.3.1(c), JBI will have no further rights and Isis will have no further obligations with respect to each terminated Drug Discovery Program.

10.3.4 **Termination After Option Exercise**. If this Agreement is terminated by a Party in accordance with this ARTICLE 10 after Option exercise, then, in addition to the terms set forth in Section 10.3.1, the following terms will apply to any Pre-Clinical Development Program that is the subject of such termination:

(a) The applicable licenses granted by Isis to JBI under this Agreement will terminate and JBI, its Affiliates and Sublicensees will cease selling the applicable Products.

(b) Neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the terminated Pre-Clinical Development Program(s).

(c) Except as explicitly set forth in Section 10.3.1(a), JBI will have no further rights and Isis will have no further obligations with respect to the terminated Pre-Clinical Development Program.

(d) If (y) JBI terminates the Agreement under Section 10.2.1 (JBI's Termination for Convenience) or (z) Isis terminates this Agreement under Section 10.2.2(b) (Isis' Right to Terminate) or Section 10.2.3 (Remedies for Failure to Use Commercially Reasonable Efforts), then the following additional terms will also apply *solely with respect to the terminated* Pre-*Clinical Development Program(s)*:

(i) JBI will grant to Isis a sublicensable, worldwide, royalty bearing exclusive license or sublicense, as the case may be, to all JBI Technology Controlled by JBI as of the date of such reversion that Covers the applicable Discontinued Product(s) solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the applicable Discontinued Product(s) in the Field (such license will be sublicensable by Isis in accordance with Section 4.1.2, *mutatis mutandis*);

(ii) For each Discontinued Product for which JBI, its Affiliate or Sublicensee has [***], Isis or any sublicensee or collaborator shall pay to JBI a royalty on net sales made by Isis or its Affiliates or sublicensee of such Discontinued Product according to the following: (a) if neither [***] prior to termination: [***]% of Net Sales, (b) if JBI, its Affiliate or Sublicensee [***] for such Discontinued Product prior to termination: [***]% of Net Sales, (c) if JBI, its Affiliate or Sublicensee [***] for such Discontinued Product prior to termination: [***]% of Net Sales, and (d) if JBI, its Affiliate or Sublicensee [***] for such Discontinued Product prior to termination: [***]% of Net Sales; provided (A) if (i) Isis enters an arms-length license agreement with a Third Party with respect to a Discontinued Product and (ii) the definition of Net Sales is different in such license agreement than as described above, then, the Parties will use the definition described in the Third Party license for the calculation of royalties under this Section 10.3.4(d)(ii); and (B) Sections 6.8.2, 6.10, 6.12 and 6.14 will govern the payment of royalties from Isis to JBI under this Section 10.3.4(d)(ii), *mutatis mutandis*.

(iii) JBI will assign to Isis any Product-Specific Patent Rights and Isis' interest in any Jointly-Owned Program Patents that, in each case relate to the applicable Discontinued Product(s) previously assigned by Isis to JBI under this Agreement;

(iv) JBI will transfer to Isis for use with respect to the Development and Commercialization of the applicable Discontinued Product(s), any Know-How data, results, regulatory information, filings, and files in the possession of JBI as of the date of such reversion to the extent related to such Discontinued Product(s), and any other information or material specified in Section 4.4;

(v) JBI will license to Isis any trademarks that are specific to a Discontinued Product(s) solely for use with such Discontinued Product(s), in accordance with Section 4.1.5, *mutatis mutandis*; *provided*, *however*, that in no event will JBI have any obligation to license to Isis any trademarks used by JBI both in connection with the Product and in connection with the sale of any other product or service, including any JBI- or JBI-formative marks; and

(vi) Isis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Program Patents arising from the terminated Pre-Clinical Development Program (or the corresponding Drug Discovery Program), and JBI will provide Isis with (and will instruct its counsel to provide Isis with) all of the information and records in JBI's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Program Patents; *provided*, *however*, if Isis intends to abandon any such Jointly-Owned Program Patents without first filing a continuation or substitution, then Isis will notify JBI of such intention at least 60 days before such Patent Right will become abandoned, and JBI will have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance thereof at its own expense with counsel of its own choice.

(e) If Isis terminates this Agreement due to JBI's material breach or JBI terminates this Agreement for convenience, upon Isis' written request pursuant to a mutually agreed supply agreement, JBI will sell to Isis any bulk API, Clinical Supplies and Finished Drug Product in JBI's possession at the time of such termination, at a price equal to JBI's cost at the time of manufacture.

(f) To the extent requested by Isis, JBI will promptly assign to Isis any manufacturing agreements identified by Isis solely to the extent related to the applicable Discontinued Products to which JBI is a party.

ARTICLE 11.
CONFIDENTIALITY

11.1 **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that, during the Agreement Term and for five years thereafter, the receiving Party (the "***Receiving Party***") and its Affiliates will keep confidential and will not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any confidential or proprietary information or materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the "***Disclosing Party***") or its Affiliates or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including trade secrets, Know-How, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to the past, present and future marketing, financial, and research and development activities of any product or potential product or useful technology of the Disclosing Party or its Affiliates and the pricing thereof (collectively, "***Confidential Information***").

11.2 **Prior Confidentiality Agreement Superseded**. As of the Effective Date, this Agreement supersedes the Confidential Disclosure Agreement executed by Isis and JBI on July 30, 2014 (including any and all amendments thereto). All information exchanged between the Parties under such Confidential Disclosure Agreement will be deemed Confidential Information hereunder and will be subject to the terms of this ARTICLE 11.

11.3 **Authorized Disclosure**. Except as expressly provided otherwise in this Agreement, a Receiving Party or its Affiliates may use and disclose to Third Parties Confidential Information of the Disclosing Party as follows: (i) solely in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement under confidentiality provisions no less restrictive than those in this Agreement, *provided*, that Confidential Information may be disclosed by a Receiving Party to a governmental entity or agency without requiring such entity or agency to enter into a confidentiality agreement; (ii) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications (subject to Section 11.4 below), complying with applicable governmental regulations, obtaining Approvals, conducting Pre-Clinical Studies or Clinical Studies, marketing the Product, or as otherwise required by applicable law, regulation, rule or legal process (including the rules of the SEC and any stock exchange); *provided*, *however*, that if a Receiving Party or any of its Affiliates is required by law or regulation to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, give reasonable advance notice to the Disclosing Party of such disclosure requirement and will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; (iii) in communication with actual or potential lenders, investors, merger partners, acquirers, consultants, or professional advisors on a need-to-know basis, in each case under confidentiality provisions no less restrictive than those of this Agreement; (iv) to the extent such disclosure is required to comply with existing expressly stated contractual obligations owed to such Party's or its Affiliates' licensor with respect to any intellectual property licensed to the other Party under this Agreement; or (v) as mutually agreed to in writing by the Parties.

11.4 Press Release; Publications; Disclosure of Agreement.

11.4.1 Announcement of Transaction. On or promptly after the Effective Date, the Parties will issue a public announcement of the execution of this Agreement in form and substance mutually agreed by the Parties and included in Schedule 11.4.

11.4.2 Other Disclosures. Except to the extent required to comply with applicable law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 11.4, neither Party nor such Party's Affiliates will make any public announcements, press releases or other public disclosures concerning a Drug Discovery Program, a Product, this Agreement or the terms or the subject matter hereof without the prior written consent of the other, which will not be unreasonably withheld, conditioned or delayed.

11.4.3 Use of Name. Except as set forth in Section 11.4.8, neither Party will use the other Party's name in a press release or other publication without first obtaining the prior consent of the Party to be named.

11.4.4 Notice of Significant Events. Each party will immediately notify (and provide as much advance notice as possible, but at a minimum two Business Days advance notice to) the other Party of any event materially related to a Product (including in such notice any disclosure of starting/stopping of a Clinical Study, clinical data or results, material regulatory discussions, filings, Approval or JBI's sales projections) so the Parties may analyze the need for or desirability of publicly disclosing or reporting such event.

11.4.5 JBI Disclosures After Option Exercise. After Option if JBI intends to make a press release or similar public communication disclosing regulatory discussions, the efficacy or safety data or results related to such Product or JBI's sales projections, (i) JBI will submit such proposed communication to Isis for review at least two Business Days in advance of such proposed public disclosure, (ii) Isis will have the right to review and recommend changes to such communication, and (iii) JBI will in good faith consider any changes that are timely recommended by Isis.

11.4.6 **Scientific or Clinical Presentations**. The Parties agree to use Commercially Reasonable Efforts to control public scientific disclosures of results of the Development activities under this Agreement to prevent any potential adverse effect of any premature public disclosure of such results. The Parties will establish a procedure for publication review and each Party will first submit to the other Party through the Joint Patent Committee an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least 45 days prior to submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication in order to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from the Drug Discovery Programs. If, during such 45-day period, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if at any time during such 45-day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party in the course of the Development under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such proposed publication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by such other Party, then such Party will either (i) delay such proposed publication for up to 60 days from the date the other Party informed such Party of its objection to the proposed publication, to permit the timely preparation and first filing of patent application(s) on the information involved or (ii) remove the identified disclosures prior to publication.

11.4.7 **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or the Product has already been publicly disclosed, either Party (or its Affiliates) may subsequently disclose the same information to the public without the consent of the other Party.

11.4.8 **Acknowledgment**. JBI will acknowledge in any press release, public presentation or publication regarding the collaboration or a Product, Isis' role in discovering and developing the Product, that the Product is under license from Isis and otherwise acknowledge Isis' contributions, and Isis' stock ticker symbol (Nasdaq: ISIS). Isis may include the Product (and identify JBI as its partner for the Product) in Isis' drug pipeline.

ARTICLE 12.
MISCELLANEOUS

12.1 **Dispute Resolution**.

12.1.1 **General.** The Parties recognize that a dispute may arise relating to this Agreement ("***Dispute***"). Except as set forth in Section 12.1.5 any Dispute, including Disputes that may involve the parent company, subsidiaries, or affiliates under common control of any Party, shall be resolved in accordance with this Section 12.

12.1.2 **Continuance of Rights and Obligations During Pendency of Dispute Resolution.** If there are any Disputes in connection with this Agreement, including Disputes related to termination of this Agreement under Section 10, all rights and obligations of the Parties shall continue until such time as any Dispute has been resolved in accordance with the provisions of this Section 12.

12.1.3 **Escalation**. Subject to Section 12.1.5, any claim, Dispute, or controversy as to the breach, enforcement, interpretation or validity of this Agreement will be referred to the Global Therapeutic Area Head, Immunology of JBI and the Chief Operating Officer of Isis (the "***Executives***") for attempted resolution. In the event the Executives are unable to resolve such Dispute within 30 days of such Dispute being referred to them, then, upon the written request of either Party to the other Party, the Dispute shall be subject to arbitration in accordance with Section 12.1.4, except as expressly set forth in Section 12.1.5 or Section 12.3.

12.1.4 **Arbitration**.

(a) If the Parties fail to resolve the Dispute through Escalation, and a Party desires to pursue resolution of the Dispute, the Dispute shall be submitted by either Party for resolution in arbitration pursuant to the then current CPR Non-Administered Arbitration Rules ("CPR Rules") (www.cpradr.org), except where they conflict with these provisions, in which case these provisions control. The arbitration will be held in Chicago, Illinois. All aspects of the arbitration shall be treated as confidential.

(b) The arbitrators will be chosen from the CPR Panel of Distinguished Neutrals, unless a candidate not on such panel is approved by both Parties. Each arbitrator shall be a lawyer with at least 15 years of experience with a law firm or corporate law department of over 25 lawyers or who was a judge of a court of general jurisdiction. To the extent that the Dispute requires special expertise, the Parties will so inform CPR prior to the beginning of the selection process.

(c) The arbitration tribunal shall consist of three arbitrators, of whom each Party shall designate one in accordance with the "screened" appointment procedure provided in CPR Rule 5.4. The chair will be chosen in accordance with CPR Rule 6.4.

(d) If, however, the aggregate award sought by the Parties is less than $5 million and equitable relief is not sought, a single arbitrator shall be chosen in accordance with the CPR Rules.

(e) Candidates for the arbitrator position(s) may be interviewed by representatives of the Parties in advance of their selection, provided that all Parties are represented.

(f) The Parties agree to select the arbitrator(s) within 45 days of initiation of the arbitration. The hearing will be concluded within nine (9) months after selection of the arbitrator(s) and the award will be rendered within 60 days of the conclusion of the hearing, or of any post hearing briefing, which briefing will be completed by both sides within 45 days after the conclusion of the hearing. In the event the Parties cannot agree upon a schedule, then the arbitrator(s) shall set the schedule following the time limits set forth above as closely as practical.

(g) The hearing will be concluded in ten hearing days or less. Multiple hearing days will be scheduled consecutively to the greatest extent possible. A transcript of the testimony adduced at the hearing shall be made and shall be made available to each Party.

(h) The arbitrator(s) shall be guided, but not bound, by the CPR Protocol on Disclosure of Documents and Presentation of Witnesses in Commercial Arbitration (www.cpradr.org) ("Protocol"). The Parties will attempt to agree on modes of document disclosure, electronic discovery, witness presentation, etc. within the parameters of the Protocol. If the Parties cannot agree on discovery and presentation issues, the arbitrator(s) shall decide on presentation modes and provide for discovery within the Protocol, understanding that the Parties contemplate reasonable discovery.

(i) The arbitrator(s) shall decide the merits of any Dispute in accordance with the law governing this Agreement, without application of any principle of conflict of laws that would result in reference to a different law. The arbitrator(s) may not apply principles such as "amiable compositeur" or "natural justice and equity."

(j) The arbitrator(s) are expressly empowered to decide dispositive motions in advance of any hearing and shall endeavor to decide such motions as would a United States District Court Judge sitting in the jurisdiction whose substantive law governs.

(k) The arbitrator(s) shall render a written opinion stating the reasons upon which the award is based. The Parties consent to the jurisdiction of the United States District Court for the district in which the arbitration is held for the enforcement of these provisions and the entry of judgment on any award rendered hereunder. Should such court for any reason lack jurisdiction, any court with jurisdiction may act in the same fashion.

(l) Each Party has the right to seek from the appropriate court provisional remedies such as attachment, preliminary injunction, replevin, etc. to avoid irreparable harm, maintain the status quo, or preserve the subject matter of the Dispute. Rule 14 of the CPR Rules does not apply to this Agreement.

(m) EXCEPT IN THE CASE OF COURT ACTIONS PERMITTED BY SECTION 12.1.5 AND FOR CLAIMS NOT SUBJECT TO ARBITRATION PURSUANT TO SECTION 12.1.4 AS SET FORTH IN SECTION 12.1.5, EACH PARTY HERETO WAIVES: (1) ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY, (2) WITH THE EXCEPTION OF RELIEF MANDATED BY STATUTE, ANY CLAIM TO PUNITIVE, EXEMPLARY, MULTIPLIED, INDIRECT, CONSEQUENTIAL OR LOST PROFITS/REVENUES DAMAGES, AND (3) ANY CLAIM FOR ATTORNEY FEES, COSTS AND PREJUDGMENT INTEREST.

(n) Each Party will bear its own attorney's fees, costs, and disbursements arising out of the arbitration, and will pay an equal share of the fees and costs of the arbitrator; *provided, however,* the arbitrator will be authorized to determine whether a Party is the prevailing party, and if so, to award to that prevailing party reimbursement for any or all of its reasonable attorneys' fees, costs and disbursements (including, for example, expert witness fees and expenses, photocopy charges, travel expenses, *etc.*), and/or the fees and costs of the Administrator and the arbitrator.

12.1.5 **Injunctive Relief; Court Actions.** Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek from any court of competent jurisdiction, in addition to any other remedy it may have at law or in equity, injunctive or other equitable relief in the event of an actual or threatened breach of this Agreement by the other Party, without the posting of any bond or other security, and such an action may be filed and maintained notwithstanding any ongoing discussions between the Parties or any ongoing arbitration proceeding. The Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive or equitable relief would be appropriate remedy. In addition, either Party may bring an action in any court of competent jurisdiction to resolve disputes pertaining to the validity, construction, scope, enforceability, infringement or other violations of Patent Rights or other intellectual property rights, and no such claim will be subject to arbitration pursuant to Section 12.1.4.

12.2 **Governing Law; Jurisdiction; Venue; Service of Process**. This Agreement and any Dispute will be governed by and construed and enforced in accordance with the laws of the State of New York, U.S.A., without reference to conflicts of laws principles.

12.3 **Recovery of Losses**. Neither Party will be entitled to recover any Losses relating to any matter arising under one provision of this Agreement to the extent that such Party has already recovered Losses with respect to such matter pursuant to other provisions of this Agreement (including recoveries under Section 9.1 or Section 9.2, and the offsets under Section 6.9.3(c)). Except for the offsets and credits explicitly set forth in Section 6.12, and Section 6.9.3(b) neither Party will have the right to set off any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

12.4 **Assignment and Successors**. Neither this Agreement nor any obligation of a Party hereunder may be assigned by either Party without the prior written consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that (i) Isis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without JBI's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction, and (ii) each Party may assign this Agreement and the rights, obligations and interests of such Party hereunder, without the other Party's consent to any Third Party purchaser of all or substantially all of its assets or all or substantially all of its assets to which this Agreement relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction with a Third Party, provided that in the event of any such transaction (whether this Agreement is actually assigned or is assumed by the acquiring Third Party or the successor corporation (as applicable) by operation of law (*e.g.*, in the context of a reverse triangular merger)), intellectual property rights of the acquiring Third Party that existed prior to such transaction shall not be included in the technology licensed hereunder or otherwise subject to this Agreement; provided that if JBI transfers or assigns this Agreement to [***] described in this Agreement, then JBI (or such Affiliate), will [***] due Isis under ARTICLE 6 for the [***] (defined below) such that Isis receives [***].

The [***].

To the extent Isis utilizes [***] in any year, Isis will [***] to JBI [***]. To assist JBI in determining when [***] pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which JBI [***] payment under this Section 12.4, and each year thereafter (including, for clarity, all years in which Isis [***], Isis will provide JBI with Isis' Annual tax returns (federal and state) and, in years in which Isis utilizes [***], supporting documentation for such [***]. Notwithstanding the foregoing, if the [***].

12.4.1 **Termination of Reporting Obligations Upon Isis Change of Control**. If there is a change in control of Isis, JBI, at its discretion, may terminate all reporting obligations regarding the Development and/or Commercialization of any Products including reporting under the Information Sharing Committee, except in all cases JBI will continue to provide the reports, audit rights and other information required under Sections 6.10, 6.11, 6.12 and 6.13.

12.5 **Force Majeure**. No Party will be held responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in performing any obligation of this Agreement when such failure or delay is due to force majeure, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, force majeure means a cause beyond the reasonable control of a Party, which may include acts of God; acts, regulations, or laws of any government; war; terrorism; civil commotion; fire, flood, earthquake, tornado, tsunami, explosion or storm; pandemic; epidemic and failure of public utilities or common carriers. In such event the Party so failing or delaying will immediately notify the other Party of such inability and of the period for which such inability is expected to continue. The Party giving such notice will be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled for up to a maximum of 90 days, after which time the Parties will negotiate in good faith any modifications of the terms of this Agreement that may be necessary to arrive at an equitable solution, unless the Party giving such notice has set out a reasonable timeframe and plan to resolve the effects of such force majeure and executes such plan within such timeframe. To the extent possible, each Party will use reasonable efforts to minimize the duration of any force majeure.

12.6 **Notices**. Any notice or request required or permitted to be given under or in connection with this Agreement will be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested), facsimile transmission (receipt verified), or overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to Isis, addressed to:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer
Fax: 760-918-3592

with a copy to:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Fax: 760-268-4922

If to JBI, addressed to:

Janssen Research & Development, LLC
Murray McKinnon, PhD1400 McKean Road
Spring House, PA 19477
Mmckinno2@its.jnj.com

with a copy to:

Chief Patent Counsel
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
Attn: Brian Carey
Bcarey2@its.jnj.com

or to such other address for such Party as it will have specified by like notice to the other Party; *provided that* notices of a change of address will be effective only upon receipt thereof. If delivered personally or by facsimile transmission, the date of delivery will be deemed to be the date on which such notice or request was given. If sent by overnight express courier service, the date of delivery will be deemed to be the next Business Day after such notice or request was deposited with such service. If sent by certified mail, the date of delivery will be deemed to be the third Business Day after such notice or request was deposited with the U.S. Postal Service.

12.7 **ISIS Reporting of This Agreement**. Isis shall provide JBI with at least [***] ([***]) days written notice of any disclosure of this document to a Third Party or to a governmental authority. The Parties agree to promptly convene to discuss such disclosure and discuss, *inter alia*, the subject matter that may be redacted prior to such submission. Notwithstanding the foregoing, Isis may (i) disclose this Agreement to Isis' legal counsel, auditors, and other professional advisors on a need-to-know basis, in each case where such advisors have agreed to confidentiality provisions no less restrictive than those of this Agreement, and (ii) may disclose the publicly available redacted version of this Agreement once such redacted version has been filed publicly with the SEC.

12.8 **Export Clause**. Each Party acknowledges that the laws and regulations of the United States restrict the export and re-export of commodities and technical data of United States origin. Each Party agrees that it will not export or re-export restricted commodities or the technical data of the other Party in any form without the appropriate United States and foreign government licenses.

12.9 **Waiver**. Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement will not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances will be construed as a continuing waiver or subsequent waiver of such condition or term or of another condition or term.

12.10 **Severability**. If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, the Parties will negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties and all other provisions hereof will remain in full force and effect in such jurisdiction and will be liberally construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability will not affect the validity, legality or enforceability of such provision in any other jurisdiction.

12.11 **Entire Agreement**. This Agreement, together with the Schedules and Appendices hereto, sets forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties and supersedes and terminates all prior agreements and understanding between the Parties. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties other than as set forth herein and therein. No subsequent alteration, amendment, change or addition to this Agreement will be binding upon the Parties hereto unless reduced to writing and signed by the respective authorized officers of the Parties.

12.12 **Independent Contractors**. Nothing herein will be construed to create any relationship of employer and employee, agent and principal, partnership or joint venture between the Parties. Each Party is an independent contractor. Neither Party will assume, either directly or indirectly, any liability of or for the other Party. Neither Party will have the authority to bind or obligate the other Party, and neither Party will represent that it has such authority.

12.13 **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, exhibit or schedule means a section of, or schedule or exhibit to this Agreement, unless another agreement is specified, (b) the word “including” (in its various forms) means “including without limitation,” (c) the words “shall” and “will” have the same meaning, (d) references to a particular statute or regulation include all rules and regulations thereunder and any predecessor or successor statute, rules or regulation, in each case as amended or otherwise modified from time to time, (e) words in the singular or plural form include the plural and singular form, respectively, (f) references to a particular Person include such Person’s successors and assigns to the extent not prohibited by this Agreement, (g) unless otherwise specified, “$” is in reference to United States dollars, and (h) the headings contained in this Agreement, in any exhibit or schedule to this Agreement and in the table of contents to this Agreement are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement.

12.14 **Books and Records**. Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees will be maintained in accordance with U.S. Generally Accepted Accounting Principles (or any successor standard), consistently applied.

12.15 **Further Actions**. Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

12.16 **Construction of Agreement**. The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement will be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

12.17 **Supremacy**. In the event of any express conflict or inconsistency between this Agreement and any Schedule or Appendix hereto, the terms of this Agreement will apply. The Parties understand and agree that the Schedules identifying the Licensed Technology are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Agreement Term, as appropriate and in accordance with the provisions of this Agreement.

12.18 **Counterparts**. This Agreement may be signed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Agreement from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

12.19 **Compliance with Laws**. Each Party will, and will ensure that its Affiliates and Sublicensees will, comply with all relevant laws and regulations in exercising its rights and fulfilling its obligations under this Agreement.

[SIGNATURE PAGE FOLLOWS]

*** - * - * - ***

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Chief Operating Officer

SIGNATURE PAGE TO RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

JANSSEN BIOTECH INC.

By: /s/ John Wilson

Name: John Wilson

Title: Vice President, Janssen Biotech Inc

SIGNATURE PAGE TO RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT

List of Appendices and Schedules

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"***Acceptance***" means, with respect to an NDA, MAA or JNDA filed for a Product, (a) in the United States, the receipt of written notice from the FDA in accordance with 21 C.F.R. §314.101(a)(2) that such NDA is officially "*filed*," (b) in the European Union, receipt by JBI of written notice of acceptance by the EMA of such MAA for filing under the centralized European procedure in accordance with any feedback received from European Regulatory Authorities; *provided that* if the centralized filing procedure is not used, then Acceptance will be determined upon the acceptance of such MAA by the applicable Regulatory Authority in a Major Country in the EU, and (c) in Japan, receipt by JBI of written notice of acceptance of filing of such JNDA from the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Additional Core IP***" means Third Party intellectual property that is necessary to [***]*; provided* Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***].

"***Affiliate***" of an entity means any corporation, firm, partnership or other entity which directly or indirectly through one or more intermediaries controls, is controlled by or is under common control with a Party to this Agreement. An entity will be deemed to control another entity if it (i) owns, directly or indirectly, at least 50% of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a foreign corporation in a particular jurisdiction) of such other entity, or has other comparable ownership interest with respect to any entity other than a corporation; or (ii) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the entity. For clarity, Regulus Therapeutics Inc. will not be deemed an "*Affiliate*" of Isis for the purposes of this Agreement under any circumstances.

"***Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Agreement Term***" has the meaning set forth in Section 10.1.

"***Alliance Manager***" has the meaning set forth in Section 1.6.5.

"***Annual***" means the period covering a Calendar Year or occurring once per Calendar Year, as the context requires.

"***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with GMP (unless expressly stated otherwise) for a Product.

"***Applicable Law***" or "***Law***" means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"***Approval***" means, with respect to a Product in any regulatory jurisdiction, approval from the applicable Regulatory Authority sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws. In jurisdictions where the applicable Regulatory Authority sets the pricing or reimbursement authorizations necessary for the general marketing and sale of such Product in the marketplace, Approval will not be deemed to have occurred if the final approval to market and sell such Product is being withheld because JBI (or its Affiliate or Sublicensee) and the Regulatory Authority have not yet determined pricing or reimbursement even if all other approvals, licenses, registrations or authorizations necessary for marketing, sale or use of such Product in such jurisdiction have been obtained. "Approval" does not include authorization by a Regulatory Authority to conduct named patient, compassionate use or other similar activities.

"***ASO***" means a single-stranded or double-stranded oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases long and is designed to hybridize to a nucleic acid transcript via the binding, partially or wholly, of such compound to the nucleic acid transcript.

"***Audit Report***" has the meaning set forth in Section 6.12.

"Autoimmune Diseases" is any of a number of diseases characterized by abnormal functioning of the immune system which causes the immune system to attack the body's own tissues. Crohn's disease and ulcerative Colitis which are inflammatory bowel diseases are included as autoimmune diseases for purposes of this Agreement.

"***Bankruptcy Code***" has the meaning set forth in Section 7.12.

"***Breaching Party***" means the Party that is believed by the Non-Breaching Party to be in material breach of this Agreement.

"***Business Day***" means any day other than a Saturday or Sunday on which banking institutions in New York, New York are open for business.

"***Calendar Quarter***" means a financial quarter based on the J&J Universal Calendar for that year (a copy of which is attached hereto as APPENDIX 3) and is used for JBI's internal and external reporting purposes; provided, however, that the first Calendar Quarter for the first Calendar Year extends from the Effective Date to the end of the then current Calendar Quarter and the last Calendar Quarter extends from the first day of such Calendar Quarter until the effective date of the termination or expiration of the Agreement.

"***Calendar Year***" means a year based on the J&J Universal Calendar for that year. The Last Calendar Year of the Term begins on the first day of the J&J Universal Calendar Year for the year during which termination or expiration of the Agreement will occur, and the last day of such Calendar Year will be the effective date of such termination or expiration.

"***Claims***" has the meaning set forth in Section 9.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase I Clinical Trial, Phase II Clinical Trial, Phase III Clinical Trial or Phase IV Clinical Trial, or such other study in humans that is conducted in accordance with good clinical practices and is designed to generate data in support or maintenance of an NDA, MAA or other similar marketing application.

"***Clinical Supplies***" means API and finished drug Product for use in a Clinical Study.

"***CMO***" means a Third Party contract manufacturer Manufacturing API, Clinical Supplies or Finished Drug Product for any purpose under this Agreement.

"***Collaboration Target***" means a gene target designated as a Collaboration Target pursuant to Section 1.2.

"***Commercialize***," "***Commercialization***" or "***Commercializing***" means any and all activities directed to marketing, promoting, detailing, distributing, importing, having imported, exporting, having exported, selling or offering to sell a Product following receipt of Approval for such Product in the applicable country, including conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of the Product and studies to provide improved formulation and Product delivery, and launching and promoting such Product in each country.

"***Commercializing Party***" means (a) JBI, with respect to a Product that is being Developed and Commercialized by or on behalf of JBI, its Affiliates or Sublicensees hereunder, and (b) Isis, with respect to a Discontinued Product that is being Developed and Commercialized by or on behalf of Isis, its Affiliates or Sublicensees hereunder.

"***Commercially Reasonable Efforts***" means the carrying out of discovery, research, development or commercialization activities using good-faith commercially reasonable and diligent efforts that the applicable Party would reasonably devote to a compound or product of similar market potential or profit potential at a similar stage in development or product life resulting from its own research efforts, based on conditions then prevailing and taking into account, without limitation, issues of safety and efficacy, regulatory authority-approved labeling, product profile, the competitiveness of alternative products in the marketplace, the likely timing of the product's entry into the market, the patent and other proprietary position, the likelihood of Approval and other relevant scientific, technical and commercial factors. Without limiting any of the foregoing, Commercially Reasonable Efforts as it applies to JBI's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to perform the "*General Activities*" described in SCHEDULE 5.2, and Commercially Reasonable Efforts as it applies to Isis' Development of a Product hereunder includes use of Commercially Reasonable Efforts to adhere to the activities and timelines set forth in each Drug Discovery Plan and Development Plan.

"***Competitive Infringement***" has the meaning set forth in Section 7.5.1.

"***Completion of PoC***" means, on a Product-by-Product basis, when JBI receives the primary end-point data generated under the statistical analysis plan of the first PoC Study.

"***Compound***" means on a Drug Discovery Program-by-Drug Discovery Program basis, any ASO that is designed to bind to the RNA that encodes the applicable Collaboration Target, where such ASO is discovered by Isis prior to or in the performance of the Drug Discovery Plan, including each Development Candidate under such Drug Discovery Program.

"***Confidential Information***" has the meaning set forth in Section 11.1. "*Confidential Information*" does not include information that:

(a) was in the lawful knowledge and possession of the Receiving Party or its Affiliates prior to the time it was disclosed to, or learned by, the Receiving Party or its Affiliates, or was otherwise developed independently by the Receiving Party or its Affiliates, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party or its Affiliates;

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party or its Affiliates;

(c) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party or its Affiliates in breach of this Agreement; or

(d) was disclosed to the Receiving Party or its Affiliates, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party or its Affiliates not to disclose such information to others.

"***Control***" or "***Controlled***" means possession of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party; *provided, however*, that if a Party has a right to grant a license or sublicense, with respect to an item of intellectual property to the other Party only upon payment of compensation (including milestones or royalties) to a Third Party ("***Third Party Compensation***") (other than Isis Supported Pass-Through Costs in the case of Isis, and other than JBI Supported Pass-Through Costs in the case of JBI), then the first Party will be deemed to have "*Control*" of the relevant item of intellectual property only if the other Party agrees to bear the cost of such Third Party Compensation. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party that becomes an Affiliate of a Party after the Effective Date (including a Third Party acquirer), no intellectual property of such Third Party will be included in the licenses granted hereunder by virtue of such Third Party becoming an Affiliate of such Party.

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that, but for a license under such patent, the act of making, using or selling would infringe a Valid Claim included in such patent, or in the case of a patent that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

"***CREATE Act***" means the Cooperative Research and Technology Enhancement Act of 2004, 35 U.S.C. § 103(c)(2)-(c)(3).

"***CTD***" has the meaning set forth in Section 5.4.1.

"Currency Hedge Rate(s)" is calculated as a weighted average hedge rate of the outstanding external foreign currency forward hedge contract(s) of Johnson & Johnson's Global Treasury Services Center (GTSC) and its Affiliates with third party banks. The hedge contract(s) is entered into to protect the transactional foreign exchange risk exposures of JBI by reducing the impact of foreign currency volatility through a systematic buildup of a yearly Currency Hedge Rate(s).

"***Develop***," "***Developing***" or "***Development***" means with respect to a Product, any and all discovery, characterization, or preclinical (including IND-Enabling Toxicology Studies), clinical, or regulatory activity with respect to the Product to seek Approval (including the submission of all necessary filings with applicable Regulatory Authorities to support such preclinical and clinical activities and Approval), including human clinical trials conducted after Approval of the Product to seek Approval for additional indications for the Product.

"Development Candidate" means a Compound that is reasonably determined by Isis' Research Management Committee in accordance with Isis' standard procedures for designating development candidates (and giving good faith consideration to the input of JBI's representatives on the JRC) as ready to start IND-Enabling Toxicology Studies. The checklist Isis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as Appendix 2.

"***Development Candidate Data Package***" means, with respect to a Development Candidate: [***].

"***Development Plan***" has the meaning set forth in Section 1.3.2(b).

"***Disclosing Party***" has the meaning set forth in Section 11.1.

"***Discontinued Product***" means a Product that is the subject of a termination under this Agreement.

"Dispositive Rejection Condition" has the meaning set forth in Section 1.2.3.

"***Dispute***" means any dispute arising between the Parties relating to, arising out of or in any way connected with this Agreement or any term or condition hereof, or the performance by either Party of its obligations hereunder, whether before or after termination of this Agreement that cannot be resolved by the Parties.

"***Drug Discovery Plan***" has the meaning set forth in Section 1.3.2(b).

"***Drug Discovery Program***" has the meaning set forth in Section 1.2.

"***Drug Discovery Term***" has the meaning set forth in Section 1.5.1.

"***Effective Date***" has the meaning set forth in the Preamble of this Agreement.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union.

"***Executives***" has the meaning set forth in Section 12.1.1.

"***FDA***" means the United States Food and Drug Administration and any successor entity thereto.

"***Field***" means, except as may be limited under Section 4.1.4, the prophylactic or therapeutic use or form of administration of a Product for any indication.

"***Finished Drug Product***" means any drug product containing API as an active ingredient in finished bulk form for the Development or Commercialization by a Party under this Agreement.

"***First Commercial Sale***" means with respect to a Product, the first sale of such Product by JBI, its Affiliate or its Sublicensee to a Third Party in a particular country after Approval of the Product has been obtained in such country.

"***Follow-On Agreement***" has the meaning set forth in Section 2.1.2.

"***Follow-On Compound***" means, with respect to a given Compound for a given Collaboration Target, any ASO (other than the Development Candidate for such Collaboration Target) that is designed to bind to the RNA that encodes such Collaboration Target discovered by or on behalf of Isis following exercise of the applicable Option by JBI.

"***FTE***" means a total of 47 weeks or 1880 hours per year of work on the Development, Manufacturing or Commercialization of a Product carried out by employees of a Party having the appropriate relevant expertise to conduct such activities.

"***FTE Rate***" Means for a given Calendar Year the rate that Isis charges for a full time equivalent [***].

"Fully Absorbed Cost of Goods" means the reasonable and necessary internal and third party costs with no mark-up incurred by Isis in making or acquiring of product as determined using the methodology set forth in SCHEDULE 4.4.4 fairly applied and as employed on a consistent basis throughout Isis' operations and shall not include inter-company profits among Isis and its Affiliates. .

"***GCP***" means the then current standards for clinical trials for pharmaceuticals, as set forth in the United States Code of Federal Regulations, ICH guidelines and applicable regulations, laws or rules as promulgated thereunder.

"***Generic Product***" means, with respect to a particular Product in a country, a generic or biosimilar pharmaceutical product, that is not produced, licensed or owned by JBI or any of its Affiliates, that:(a) contains the same, or a bioequivalent of the, active ingredient as a Product; and (b) is approved for use in such country by a regulatory authority through a regulatory pathway by referencing clinical data first submitted for obtaining regulatory approval for such Product. Generic Product includes any pharmaceutical products obtained via a bioequivalence or bioavailability showing such as those covered by section 505(b)(2) or under 505(j) of the U.S. Federal Food, Drug, and Cosmetic Act or an equivalent outside the United States.

"***GLP***" means the then-current good laboratory practice standards promulgated or endorsed by the FDA as defined in 21 C.F.R. Part 58, and comparable foreign regulatory standards.

"***GMP***" means current Good Manufacturing Practices as specified in the United States Code of Federal Regulations, ICH Guideline Q7A, or equivalent laws, rules, or regulations of an applicable Regulatory Authority at the time of manufacture.

"[***].

"***IND***" means an Investigational New Drug Application (as defined in the Food, Drug and Cosmetic Act, as amended) filed with the FDA or its foreign counterparts.

"***IND-Enabling Toxicology Studies***" means the pharmacokinetic and toxicology studies required to meet the requirements for filing an IND. IND-Enabling Toxicology Studies do not include chronic toxicology studies or reproductive toxicology studies.

"***Indemnitee***" has the meaning set forth in Section 9.3.

"***Indication***" means distinct, well-categorized disease or condition in humans for which a separate marketing authorization (or amendment to a marketing authorization) is required.

"***Initiation***" or "***Initiate***" means, with respect to any IND-Enabling Toxicology Study, dosing of the first animal subject in such IND-Enabling Toxicology Study and, with respect to any Clinical Study, dosing of the first human subject in such Clinical Study.

"***Integrated Development Plan***" or "***IDP***" has the meaning set forth in Section 5.3.

"***Isis***" has the meaning set forth in the Preamble of this Agreement.

"***Isis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Isis Product-Specific Patents or Isis Manufacturing and Analytical Patents. A list of Isis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 8.2.2(a) attached hereto.

"***Isis Formulation Patents***" means the Patent Rights listed on Schedule 8.2.2(d) attached hereto.

"***Isis In-License Agreements***" has the meaning set forth in Section 6.9.1(a).

"***Isis Internal ASO Safety Database***" has the meaning set forth in Section 5.6.

"***Isis Know-How***" means any Know-How, including any Jointly-Owned Program Know-How and Isis Program Know-How, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Know-How does not include the Isis Manufacturing and Analytical Know-How.

"***Isis Manufacturing and Analytical Know-How***" means Know-How, including Jointly-Owned Program Know-How, that relates to the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. Isis Manufacturing and Analytical Know-How does not include the Isis Know-How.

"***Isis Manufacturing and Analytical Patents***" means Patent Rights, including Jointly-Owned Program Patents, that claim methods and materials used in the synthesis or analysis of a Product regardless of sequence or chemical modification, owned, used, developed by, or licensed to Isis or its Affiliates, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Manufacturing and Analytical Patents as of the Effective Date is set forth on SCHEDULE 8.2.2(b) attached hereto. Isis Manufacturing and Analytical Patents do not include the Isis Product-Specific Patents or the Isis Core Technology Patents.

"***Isis Platform Technology***" has the meaning set forth in Section 8.2.2.

"***Isis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Isis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Isis Product-Specific Patents as of the Effective Date is set forth on SCHEDULE 8.2.2(c) attached hereto.

"***Isis Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Isis Program Patents***" has the meaning set forth in Section 7.1.2.

"***Isis Supported Pass-Through Costs***" means [***].

"***JBI***" has the meaning set forth in the Preamble of this Agreement.

"***JBI Royalty***" has the meaning set forth in Section 6.8.1.

"***JBI Know-How***" means any Know-How owned, used, developed by, or licensed to JBI or its Affiliates, in each case to the extent Controlled by JBI or its Affiliates on the Effective Date or at any time during the Agreement Term, *but specifically excluding* the JBI Program Know-How.

"***JBI Patents***" means any Patent Rights included in the JBI Technology.

"***JBI Product-Specific Patents***" means all Product-Specific Patents owned, used, developed by, or licensed to JBI or its Affiliates, in each case to the extent Controlled by JBI or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***JBI Program Know-How***" has the meaning set forth in Section 7.1.2.

"***JBI Program Patents***" has the meaning set forth in Section 7.1.2.

"***JBI Program Technology***" has the meaning set forth in Section 7.1.2.

"***JBI-Prosecuted Patents***" has the meaning set forth in Section 7.2.4.

"***JBI Supported Pass-Through Costs***" means [***].

"***JBI Technology***" means the JBI Program Technology, Jointly-Owned Program Technology, JBI Product-Specific Patents and any trademarks described in Section 4.1.5, owned, used, developed by, or licensed to JBI or its Affiliates that is necessary or useful to Develop, register, Manufacture or Commercialize a Product.

"***Japan NDA***" or "***JNDA***" means the Japanese equivalent of an NDA filed with the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***JNDA Approval***" means the Approval of a JNDA by the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto) for the applicable Product in Japan including pricing.

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 7.1.3(a).

"***Jointly-Owned Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Jointly-Owned Program Patents***" has the meaning set forth in Section 7.1.2.

"***Jointly-Owned Program Technology***" has the meaning set forth in Section 7.1.2.

"***JRC***" has the meaning set forth in Section 1.6.1.

"***Know-How***" means inventions, technical information, know-how and materials, including technology, data, compositions, formulas, biological materials, assays, reagents, constructs, compounds, discoveries, procedures, processes, practices, protocols, methods, techniques, results of experimentation or testing, knowledge, trade secrets, skill and experience, in each case whether or not patentable or copyrightable, and in each case that are unpatented.

"***Lead Party***" has the meaning set forth in Section 7.4.1.

"***Licensed Know-How***" means Isis Manufacturing and Analytical Know-How, and Isis Know-How. For clarity, Licensed Know-How does not include any Know-How covering delivery devices.

"***Licensed Patents***" means the Isis Product-Specific Patents, Isis Core Technology Patents, Isis Manufacturing and Analytical Patents, Isis Formulation Patents and Isis' interest in Jointly-Owned Program Patents. For clarity, Licensed Patents do not include any Patent Rights claiming formulation technology or delivery devices unless such Patent Rights are included in the Jointly-Owned Program Patents.

"***Licensed Technology***" means, on a Product-by-Product basis, any and all Licensed Patents, Licensed Know-How, and any trademarks described in Section 4.1.5, to the extent necessary or useful to Develop, register, Manufacture or Commercialize such Product.

"***Losses***" has the meaning set forth in Section 9.1.

"***MAA***" means, with respect to a particular Product, a marketing authorization application filed with the EMA after completion of Clinical Studies (excluding Phase IV Clinical Trials) to obtain Approval for such Product under the centralized European filing procedure or, if the centralized EMA filing procedure is not used, filed using the applicable procedures in any European Union country.

"***MAA Approval***" means, with respect to a particular Product, the Approval of an MAA by the EMA for such Product in any country in the EU including pricing.

"***Major Market***" means any of the following countries: the United States, Japan, the United Kingdom, Germany, France, Italy and Spain.

"***Manufacture***" or "***Manufactured***" or "***Manufacturing***" means any activity involved in or relating to the manufacturing, quality control testing (including in-process, release and stability testing), releasing or packaging, for pre-clinical and clinical purposes, of API or a Product in finished form.

"***Milestone Event***" means a Pre-Licensing Milestone Event or a Post-Licensing Milestone Event, as the case may be.

"***Minimum Third Party Payments***" means [***].

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Studies to obtain Approval for a Product in the United States.

"***NDA Approval***" means the Approval of an NDA by the FDA for a Product in the U.S.

"***Negotiation Period***" has the meaning set forth in Section 2.1.2.

"***Net Sales***" means the gross amounts invoiced on sales of a Product by JBI or any of its Affiliates or sublicensees to a Third Party purchaser in an arms-length transaction, less the following customary deductions, determined in accordance with US generally accepted accounting principles and standard internal policies and procedures and accounting standards consistently applied throughout Johnson & Johnson, to the extent specifically and solely allocated to such Product and actually taken, paid, accrued, allowed, included or allocated based on good faith estimates in the gross sales prices with respect to such sales (and consistently applied as set forth below):

a) normal and customary trade, cash and/or quantity discounts, allowances, and credits allowed or paid, in the form of deductions actually allowed or fees actually paid with respect to sales of such Product (to the extent not already reflected in the amount invoiced) excluding commissions for commercialization;
b) excise taxes, use taxes, tariffs, sales taxes and customs duties, and/or other government charges imposed on the sale of Product to the extent included in the price and separately itemized on the invoice price (but specifically excluding, for clarity, any income taxes assessed against the income arising from such sale) (including VAT, but only to the extent that such VAT taxes are not reimbursable or refundable);
c) outbound freight, shipment and insurance costs to the extent included in the price and separately itemized on the invoice price;

d) compulsory payments and cash rebates related to the sales of such Product paid to a Governmental Authority (or agent thereof) pursuant to governmental regulations by reason of any national or local health insurance program or similar program, to the extent allowed and taken; including Government levied fees as a result of Healthcare Reform policies
e) retroactive price reductions, credits or allowances actually granted upon rejections or returns of Product, including for recalls or damaged good and billing errors; and
f) rebates, chargebacks, and discounts (or equivalent thereof) actually granted to managed health care organizations, pharmacy benefit managers (or equivalent thereof), federal, state/provincial, local or other governments, or their agencies or purchasers, reimbursers, or trade customers.

The sales of Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Royalty Period.

All aforementioned deductions shall only be allowable to the extent they are commercially reasonable and shall be determined, on a country-by-country basis, as incurred in the ordinary course of business in type and amount consistent with the Party's, the Affiliate's, or Third Party sublicensee's (as the case may be) business practices consistently applied across its product lines and accounting standards and verifiable based on the Johnson & Johnson sales reporting system. All such discounts, allowances, credits, rebates, and other deductions shall be fairly and equitably allocated to Product and other products of the Party and its Affiliates and sublicensees such that Product does not bear a disproportionate portion of such deductions.

The following shall be excluded for the purposes of calculating royalties or sales milestones:

a) Sales of Product by and between JBI and its Affiliates and sublicenses so long as such Product is subsequently resold to a Third-party end user where such resale to such Third-party end user is included in Net Sales
b) Sales of Product for the use in conducting clinical trials, pre-clinical studies or other research or development activities in a country in order to obtain Regulatory Approval of Product in such country
c) Product provided free of charge for a *bona fide* charitable purpose
d) Product used for commercially reasonable free sampling programs.
e) Sales of Product free of charge for Compassionate
f) Sales of Product for Named Patient Sales where such Product is sold at a significant discount to the proposed price for the Product following Approval.

In the event Product(s) are sold in combination with other products or services from JBI, its Affiliates or sublicensees and the customer receives a specific discount for such "bundling" of products (for clarity, this situation describes bundling of two or more separate products, each in finished dosage form, and not a fixed combination of two active pharmaceutical ingredients), the Net Sales of the said Product(s), for the purposes of determining royalty payments, shall be determined by multiplying the relevant Net Sales by the fraction, A/(A+B) where A is the weighted (by sales volume) average sale price in a particular country of the Product(s) in the previous Calendar Year when sold separately and B is the weighted average sale price in that country in the previous Calendar Year of the other product sold separately. In the event that such average sale price cannot be determined for either of the Product(s) or the other product(s) it has been sold with, in combination, then for purposes of determining the royalty payments, JBI will propose a reasonable good faith estimate of the fair market value of each component (and JBI will provide Isis a justification and support for such estimates) which will be substituted for the weighted average sales price for each such product in the formula above. If JBI, its Affiliate or a Sublicensee receives non-monetary consideration for a Product, Net Sales are calculated based on the fair market value of that consideration.

"***New Third Party Licenses***" has the meaning set forth in Section 8.3.2.

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***Option***" has the meaning set forth in Section 3.1.

"***Option Deadline***" has the meaning set forth in Section 3.1.

"***Option Period***" means, with respect to a Drug Discovery Program, the period beginning on the date when the applicable Collaboration Target was designated and ending on the expiration or earlier termination of the Option with respect to such Drug Discovery Program.

"***Out-of-Pocket Expenses***" means the amounts paid to Third Party vendors or contractors, for services or materials provided by them directly in the performance of activities to the extent such services or materials apply directly to the activities under this agreement.

"***Party***" or "***Parties***" means JBI and Isis individually or collectively.

"***Patent Costs***" means the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other reasonable Out-of-Pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patent Rights.

"***Patent Rights***" means (a) patents, patent applications and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, divisionals, continuations, substitutions, continuations-in-part of and similar applications claiming priority to any of the foregoing, and (c) all patents and similar government-issued rights protecting inventions issuing on any of the foregoing applications, together with all registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions of any of (a), (b) or (c).

"***Permitted Licenses***" means (1) licenses granted by Isis before or after the Effective Date to any Third Party under the Isis Core Technology Patents, the Isis Manufacturing and Analytical Patents, or the Isis Manufacturing and Analytical Know-How (but not under the Isis Product-Specific Patents) to (a) use oligonucleotides (or supply oligonucleotides to end users) solely to conduct pre-clinical research, or (b) enable such Third Party to manufacture or formulate oligonucleotides, where (i) such Third Party is primarily engaged in providing contract manufacturing or services and is not primarily engaged in drug discovery, development or commercialization of therapeutics; and (ii) Isis does not assist such Third Party to identify, discover or make a Compound or Product; and (2) material transfer, collaboration or sponsored research agreements with academic collaborators or non-profit institutions solely to conduct noncommercial research.

"***Person***" will mean any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau or agency, any other entity or body, or an individual.

"***Phase I Clinical Trial***" means a human clinical trial that is intended to initially evaluate the safety, metabolism and pharmacokinetics of a therapeutic agent that would otherwise satisfy the requirements of 21 C.F.R. 312.21(a) or an equivalent clinical trial in a country in the Territory other than the United States.

"***Phase II Clinical Trial***" means a human clinical trial, for which the primary endpoints include a determination of safety, dose ranges or an indication of efficacy of a therapeutic in patients being studied as described in 21 C.F.R. §312.21(b), or an equivalent clinical trial in a country in the Territory other than the United States, and that is prospectively designed to generate sufficient data (if successful) to commence pivotal clinical trials.

"***Phase III Clinical Trial***" means a human clinical trial (regardless of whether actually designated as "Phase III") that is prospectively designed, along with other Phase III Clinical Trials, to demonstrate statistically whether a therapeutic is safe and effective for use in humans in the indication being investigated as described in 21 C.F.R. §312.21(c), or an equivalent clinical trial in a country in the Territory other than the United States.

"***Phase IV Clinical Trial***" means, with respect to a Product, (a) any Clinical Study conducted to satisfy a requirement of a Regulatory Authority in order to maintain a Regulatory Approval for such Product or (b) any Clinical Study conducted after the first Regulatory Approval in the same disease state for which such Product received Regulatory Approval other than for purposes of obtaining Regulatory Approval.

"***Plan***" means a Drug Discovery Plan and/or Development Plan, as applicable.

"PoC Study" means a study conducted during a Phase II Clinical Trial designed to give preliminary evidence of efficacy and safety for a Product.

"***Post-Licensing Milestone Event***" has the meaning set forth in Section 6.4.

"***Pre-Clinical Studies***" means *in vitro* and *in vivo* studies of a Product, not in humans, including those studies conducted in whole animals and other test systems, designed to determine the toxicity, bioavailability, and pharmacokinetics of such Product and whether such Product has a desired effect.

"***Pre-Licensing Milestone Event***" has the meaning set forth in Section 6.2.

"***Prior Agreements***" means the Agreements listed on Schedule 8.2.2(e) attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means, on a Drug Discovery Program-by-Drug Discovery Program basis, a finished drug product containing a unique and specific Compound as an active pharmaceutical ingredient. Each Product shall contain a different specific Compound (s).

"***Product-Specific Patents***" means Patent Rights Controlled by a Party or any of its Affiliates on or after the Effective Date, including any Program Patents, claiming (i) the specific composition of matter of a Product, or (ii) methods of using a Product as a prophylactic or therapeutic; *provided however*, Patent Rights Controlled by Isis or any of its Affiliates that (y) include claims that are directed to subject matter applicable to ASOs in general, or (z) include an ASO, the sequence of which targets the RNA that encodes a Collaboration Target and the RNA of a gene that does not encode a Collaboration Target, will not be considered Product-Specific Patents, and in the case of (y) and (z), such Patent Rights will be considered Isis Core Technology Patents.

"***Program Patents***" has the meaning set forth in Section 7.1.2.

"***Prosecution and Maintenance***" or "***Prosecute and Maintain***" means, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as handling re-examinations, reissues, and requests for patent term extensions with respect to such Patent Right, together with the conduct of interferences, the defense of oppositions and other similar proceedings with respect to the particular Patent Right. For clarification, "***Prosecution and Maintenance***" or "***Prosecute and Maintain***" will not include any other enforcement actions taken with respect to a Patent Right.

"***Receiving Party***" has the meaning set forth in Section 11.1.

"***Regulatory Approval***" means the approval necessary for the commercial manufacture, distribution, marketing, promotion, offer for sale, use, import, export, and sale of a pharmaceutical product in a jurisdiction regulated by a Regulatory Authority.

"***Regulatory Authority***" means any governmental authority, including the FDA, EMA or Koseisho (*i.e.*, the Japanese Ministry of Health and Welfare, or any successor agency thereto), that has responsibility for granting any licenses or approvals or granting pricing or reimbursement approvals necessary for the marketing and sale of a Product in any country.

"***Research***" means conducting the research activities with Compounds as set forth in each Drug Discovery Plan, including pre-clinical research and lead optimization, *but specifically excluding* Development and Commercialization. When used as a verb, "*Researching*" means to engage in Research.

"***RMC***" means Isis' Research Management Committee, or any successor committee.

"***ROFN Period***" has the meaning set forth in Section 2.1.2.

"***ROFN Termination Event***" has the meaning set forth in Section 2.1.2.

"***Royalty Period***" has the meaning set forth in Section 6.8.2(a).

"***Sales Milestone Event***" has the meaning provided in Section 6.7.

"[***].

"***Specific Performance Milestone Event***" has the meaning set forth in Section 5.2.

"***Step-In Party***" has the meaning set forth in Section 7.4.1.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed Technology or JBI Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Substitution Fee"*** means $[***] per substituted target to be paid by JBI following Isis' acceptance of JBI's proposed substitute gene target under Section 1.2.5 **.**

"***Supplemental Information***" has the meaning provided in Section 1.3.5.

"***Target Nomination Period***" has the meaning set forth in Section 1.2.1.

[***] "***Third Party***" means a Person or entity other than the Parties or their respective Affiliates.

"***Third Party Obligations***" means any financial and non-financial encumbrances, obligations, restrictions, or limitations imposed by an agreement between Isis and a Third Party (including the Isis In-License Agreements) that relate to a Product, a Collaboration Target, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***United States***" or "***U.S.***" means the fifty states of the United States of America and all of its territories and possessions and the District of Columbia.

"***Valid Claim***" means a claim (i) of any issued, unexpired United States or foreign Patent Right, which will not, in the country of issuance, have been donated to the public, disclaimed, nor held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) of any United States or foreign patent application within a Patent Right, which will not, in the country in question, have been cancelled, withdrawn, abandoned nor been pending for more than six years, not including in calculating such six-year period time in which such application is in interference or opposition or similar proceedings or time in which a decision of an examiner is being appealed. Notwithstanding the foregoing, on a country-by-country basis, a patent application pending for more than six years will not be considered to have any Valid Claim for purposes of this Agreement unless and until a patent meeting the criteria set forth in clause (i) above with respect to such application issues.

APPENDIX 2

DEVELOPMENT CANDIDATE CHECKLIST

- Development path identified
- Adequate Potency/ Efficacy/Tolerability in preclinical models
- Proof of Antisense Mechanism for Candidate
- Liver/Kidney PK Ratio: Rat
- Liver/Kidney PK Ratio: Monkey
- hPBMC Assay
- Mouse Tolerability
- Rat Tolerability
- Monkey Tolerability
- Off-Target Potential
- SNP Analysis
- Viscosity
- Intellectual Property

APPENDIX 3

J&J Universal Calendar

2015 UNIVERSAL CALENDAR

	M	T	W	T	F	S	S
	29	30	31				
JAN				1	2	3	4
(4 Weeks)	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30	31	
FEB							1
(4 Weeks)	2	3	4	5	6	7	8
	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	
							1
MAR	2	3	4	5	6	7	8
(5 Weeks)	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30	31					
APR			1	2	3	4	5
(4 Weeks)	6	7	8	9	10	11	12
	13	14	15	16	17	18	19
	20	21	22	23	24	25	26
	27	28	29	30			
MAY					1	2	3
(4 Weeks)	4	5	6	7	8	9	10
	11	12	13	14	15	16	17
	18	19	20	21	22	23	24
	25	26	27	28	29	30	31
JUN	1	2	3	4	5	6	7
(5 Weeks)	8	9	10	11	12	13	14
	15	16	17	18	19	20	21
	22	23	24	25	26	27	28

	M	T	W	T	F	S	S
	29	30					
JUL			1	2	3	4	5
(4 Weeks)	6	7	8	9	10	11	12
	13	14	15	16	17	18	19
	20	21	22	23	24	25	26
	27	28	29	30	31		
AUG						1	2
(4 Weeks)	3	4	5	6	7	8	9
	10	11	12	13	14	15	16
	17	18	19	20	21	22	23
	24	25	26	27	28	29	30
	31						
SEP		1	2	3	4	5	6
(5 Weeks)	7	8	9	10	11	12	13
	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
	28	29	30				
OCT				1	2	3	4
(4 Weeks)	5	6	7	8	9	10	11
	12	13	14	15	16	17	18
	19	20	21	22	23	24	25
	26	27	28	29	30	31	
NOV							1
(4 Weeks)	2	3	4	5	6	7	8
	9	10	11	12	13	14	15
	16	17	18	19	20	21	22
	23	24	25	26	27	28	29
	30						
DEC		1	2	3	4	5	6
(6 Weeks)	7	8	9	10	11	12	13
	14	15	16	17	18	19	20
	21	22	23	24	25	26	27
	28	29	30	31			
					1	2	3

SCHEDULE 1.6.1

JRC GOVERNANCE

(a) The JRC will determine the JRC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The JRC will codify these operating procedures in the written minutes of the first meeting.

(b) The JRC may hold meetings in person or by audio or video conference as determined by the JRC; but at least two meetings per year will be in person (one held at Isis' facilities, and the other held at JBI's facilities in the U.S.). Alliance Managers will attend JRC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend JRC meetings, including any subject matter expert(s) with valuable knowledge of Collaboration Targets or the diseases associated with such Collaboration Targets.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that JRC meetings occur, JRC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.6.3, Section 7.1.3 and Section 12.1, as applicable.

(d) The JRC members from the same Party will collectively have one vote. The JRC will strive to make recommendations with approval of both Isis members and JBI members, and record such recommendations in the minutes of the applicable JRC meeting.

(e) The JRC may form subcommittees and working groups as it determines in order to carry out its activities under this Agreement, all of which will dissolve when the JRC dissolves.

SCHEDULE 1.6.5

Alliance Management Activities

Each Alliance Manager is responsible for:

(a) Promoting the overall health of the relationship between the Parties;

(b) Developing a mutually agreed alliance launch plan covering any activities and systems that the Parties need to implement within the first 100 days after the Effective Date to support the Drug Discovery Programs;

(c) Organizing JRC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the JRC with organization of meetings, information exchange, meeting minutes, and facilitating dispute resolution as necessary;

(e) Preparing status and progress reports on the above as determined necessary by the JRC;

(f) Ensuring compliance in maintaining the Isis Internal ASO Safety Database as outlined in Section 5.6;

(g) Ensuring proper approval of publications prior to submission as required in Section 11.4; and

(h) Understanding and communicating the components contained in the relationship-management document provided by Isis to JBI, to assist JBI in understanding and complying with the contractual obligations under the Isis In-License Agreements after Option exercise.

SCHEDULE 4.4.4

Isis' Fully Absorbed Cost of Goods Methodology
[***]

SCHEDULE 5.2

JBI's Development and Commercialization Activities

[***]

SCHEDULE 6.9.1

Certain Isis In-License Agreements

(Relevant to the Drug Discovery Programs as of the Effective Date)

[***]

SCHEDULE 8.2.2(a)

Isis Core Technology Patents

[***]

SCHEDULE 8.2.2(b)

Isis Manufacturing and Analytical Patents

[***]

SCHEDULE 8.2.2(c)

Isis Product-Specific Patents

[***]

SCHEDULE 8.2.2(d)

Isis Formulation Patents

[***]

SCHEDULE 8.2.2(E)

Prior Agreements

[***]

Schedule 11.4 – Press Release

ISIS PHARMACEUTICALS ANNOUNCES COLLABORATION WITH JANSSEN TO DISCOVER AND DEVELOP RNA-TARGETED THERAPEUTICS FOR AUTOIMMUNE DISEASES IN THE GI TRACT

-- Collaboration Combines Isis' RNA-Targeted Technology with Expertise of Janssen in Autoimmune Disorders and Therapeutic Formulation --

Carlsbad, Calif., Jan. [5], 2015 –Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) today announced that the company has entered into a global collaboration with Janssen Biotech, Inc. (Janssen) to discover and develop antisense drugs to treat autoimmune disorders of the gastrointestinal (GI) tract. The collaboration brings together Isis' RNA-targeted technology platform and the expertise of Janssen in autoimmune disorders and therapeutic formulation to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders in the GI tract.

"We are excited to be working with Janssen to apply our drug discovery and development efforts in this therapeutic area. This collaboration broadens the utility of our drug discovery technology to new targets in the GI tract and expands the administration of antisense drugs to local delivery, including oral delivery, to the gut," said B. Lynne Parshall, chief operating officer at Isis Pharmaceuticals. "We are the leader in RNA-targeted therapeutics and our innovation and the successes of our pipeline drugs enable us to form collaborations, like this one, with leaders in specific therapeutic areas. This partnering strategy ensures that we have access to resources that support and enhance our drug discovery efforts and also provides us with collaborators, like Janssen, who are uniquely capable of conducting development, marketing and commercial efforts for these drugs. ."

Under the terms of the agreement, which covers three programs, Isis will receive $35 million in upfront payments, including a payment to initiate human lead optimization on the first collaboration target. Isis is eligible to receive nearly $800 million in development, regulatory and sales milestone payments and license fees for these programs. In addition, Isis will receive tiered royalties that on average are double-digits on sales from any product that is successfully commercialized. Janssen has the option to license a drug from each of the programs once a development candidate is identified. If Janssen exercises its option, it will assume global development, regulatory and commercialization responsibilities.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its leadership position in RNA-targeted technology to discover and develop novel drugs for its product pipeline and for its partners. Isis' broad pipeline consists of 34 drugs to treat a wide variety of diseases with an emphasis on cardiovascular, metabolic, severe and rare diseases, including neurological disorders, and cancer. Isis' partner, Genzyme, is commercializing Isis' lead product, KYNAMRO®, in the United States and other countries for the treatment of patients with homozygous FH. Isis has numerous drugs in Phase 3 development in severe and rare and cardiovascular diseases. These include a ISIS-APOCIII$_{Rx}$, a drug Isis is developing to treat patients with severely high triglycerides, such as patients with familial chylomicronemia syndrome; ISIS-TTR$_{Rx}$, a drug Isis is developing with GSK to treat patients with the polyneuropathy form of TTR amyloidosis; and, ISIS-SMN$_{Rx}$, a drug Isis is developing with Biogen Idec to treat infants and children with spinal muscular atrophy, a severe and rare neuromuscular disease. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis' alliance with Janssen, Isis' research, development and commercial opportunities in developing antisense drugs to treat inflammatory bowel disease. Any statement describing Isis' 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 drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2013, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

Isis Pharmaceuticals' Contacts:

D. Wade Walke, Ph.D.
Vice President, Corporate Communications and Investor Relations
760-603-2741

Amy Blackley, Ph.D.
Associate Director, Corporate Communications
760-603-2772

###

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 "[***]".

Exhibit 10.56

December 21, 2016

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel

Re: *First Amendment To Research Collaboration, Option and License Agreement of December 22, 2014*

Dear Madame or Sir:

Reference is made to the Research Collaboration, Option and License Agreement of December 22, 2014 (the "***Agreement***"), by and between Janssen Biotech Inc. ("***JBI***"), and Ionis Pharmaceuticals, Inc. (formerly Isis Pharmaceuticals, Inc.; hereinafter "***Ionis***"), or individually as "***Party***" or collectively as "***Parties***." This document is a "***First Amendment***" to the Agreement and the "***First Amendment Effective Date***" shall be the date of the last signature below.

In general, the Parties agreed to modify the Agreement to reflect alignment on the terms and conditions which will enable JBI to propose, and for Ionis to accept, a third target (**[***]**), and for JBI to Develop and Commercialize an **[***]** Compound that JBI selects as the JBI **[***]** Development Candidate. This First Amendment includes changes to the companion financials and describes the consideration associated with entering into this First Amendment.

To effectuate the agreed upon changes, the Parties agree to the provisions described herein.

Definitions. The Parties agree to introduce new definitions to the Agreement as follows:

"***GLP Toxicology Study***" means a GLP toxicology study necessary to meet the requirements for filing an IND.

"***Ionis* [***] *Field***" means any prophylactic, therapeutic or other use or form of administration of any ASO that is designed to bind to the RNA that encodes **[***]** for any indication other than treatment of a disease of the gastrointestinal tract.

"**[***]**" means the gene, **[***]**.

"**[***]** ***Compound***" means any ASO that is designed to bind to the RNA that encodes **[***]**, where such ASO is discovered by Ionis prior to **[***]**, including **[***]**.

"***IONIS*-[***]$_{Rx}$**" means the compound known as **[***]**.

"***JBI* [***] *Development Candidate***" means the **[***]** Compound selected by JBI. Such JBI **[***]** Development Candidate will be a "*Product*" under the Agreement.

"***JBI* [***] *Field***" means **[***]** delivery of the JBI **[***]** Development Candidate for treatment of diseases of the gastrointestinal tract, ***unless*** expanded to include the Expanded GI Field.

Defined terms used but not defined herein have the meaning ascribed to such terms in the Agreement.

Agreement Provisions

Confirmation - Section 1.2.3 – JBI proposed a third gene target designated **[***]** and Ionis accepts this designation.

Confirmation - Section 1.2.4 – **[***]** is now a Collaboration Target.

Amendment of Section 2.1.3 – Section 2.1.3 of the Agreement is amended to include a new item (e) as follows:

"(e) The research, development, manufacture, commercialization or other exploitation of IONIS-**[***]**$_{Rx}$ or any other ASO that is designed to bind to the RNA that encodes **[***]**, in each case by Ionis independently or for or with any of its Affiliates or any Third Party (including the grant of any license to any Third Party), in each case in the Ionis **[***]** Field."

Amendment of Section 4.1.1 Solely with respect to the JBI [***] Development Candidate – The Parties agree that, solely with respect to the JBI **[***]** Development Candidate, Section 4.1.1 of the Agreement is deleted in its entirety and replaced with the following language:

"**4.1.1 Development and Commercialization License**. Subject to the terms and conditions of this Agreement, effective upon JBI's exercise of the Option for the JBI **[***]** Development Candidate in accordance with this Agreement, Ionis grants to JBI (i) a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Isis Product Specific Patents to Research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize the JBI **[***]** Development Candidate in the JBI **[***]** Field, and (ii) a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology other than the Isis Product Specific Patents to Research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize the JBI **[***]** Development Candidate in the JBI **[***]** Field. The grants described under subsection (i) and subsection (ii) in no way limit Ionis' ability to grant additional licenses to Third Parties under the Licensed Technology in the Ionis **[***]** Field."

Addition of New Section 4.1.6 – [***] Administration of JBI [***] Development Candidate. The Parties acknowledge that the JBI **[***]** Field is initially limited to **[***]** delivery of the JBI **[***]** Development Candidate for treatment of diseases of the gastrointestinal tract. Following JBI's exercise of its Option for the JBI **[***]** Development Candidate but prior to **[***]** **[***]** with the JBI **[***]** Development Candidate, JBI may elect to expand the JBI **[***]** Field to include the **[***]** delivery of the JBI **[***]** Development Candidate for the treatment of diseases of the gastrointestinal tract ("***Expanded GI Field***") by providing the JRC written notice of such **[***]** election. Within **[***]** days after timely providing such election notice to the JRC:

a) In the case where JBI selected IONIS-**[***]**$_{Rx}$** as the JBI **[***]** Development Candidate and, as of the date the JRC receives such election notice, Ionis has **[***]**, then JBI's rights under this Section 4.1.6 shall be limited to a right to negotiate with Ionis in good faith regarding both (i) **[***]** and (ii) **[***]**; or

b) In the case where (x) JBI selected IONIS-**[***]**$_{Rx}$** as the JBI **[***]** Development Candidate but, as of the date the JRC receives such election notice, Ionis *has not* **[***]**, or (y) JBI did not select IONIS-**[***]**$_{Rx}$** as the JBI **[***]** Development Candidate, the Parties shall negotiate in good faith both (i) **[***]**.

The JBI **[***]** Field will only be expanded to include the Expanded GI Field if the Parties mutually agree on the **[***]** described in subsection (a) or (b) in this Section 4.1.6 (as applicable). If JBI progresses a JBI **[***]** Development Candidate in the Expanded GI Field all other provisions of the Agreement shall apply to the Expanded GI Field and Net Sales from **[***]** delivered and a **[***]** delivered JBI **[***]** Development Candidate will be aggregated when calculating payments due under the Agreement royalty tiers.

Addition of New Section 5.7 - **Development and Commercialization Cooperation.** If JBI selects IONIS-**[***]**$_{Rx}$** as the JBI **[***]** Development Candidate, then within **[***]** (**[***]**) months after JBI exercises its Option, the Parties will convene to negotiate commercially reasonable terms for managing the continued Development and Commercialization of IONIS-**[***]**$_{Rx}$** by both Parties, including procedures for the mutual exchange of **[***]** and **[***]** information associated with IONIS-**[***]**$_{Rx}$.

Addition of New Section 5.8 – Back-Up JBI [***] Development Candidate. If JBI has exercised its Option for the JBI **[***]** Development Candidate and subsequently delivers written notice to Ionis that JBI will discontinue Development of such JBI **[***]** Development Candidate for reasons of **[***]** (e.g., **[***]** or **[***]** issues), then, upon JBI's written request to Ionis, JBI may select as a replacement of such JBI **[***]** Development Candidate any other **[***]** Compound ("***Back-Up* [***] *Development Candidate***") that is not being developed or commercialized (i.e., such **[***]** Compound has at least started a **[***]**) by Ionis, its Affiliates or its sublicensee as of the date Ionis receives such request from JBI. JBI will select any such Back-Up **[***]** Development Candidate within **[***]** days following the date Ionis receives the discontinuation notice and, unless mutually agreed by Ionis, JBI will be **[***]**. Upon any such selection of a Back-Up **[***]** Development Candidate, such Back-Up **[***]** Development Candidate will become the "*JBI* **[***]** *Development Candidate*" and a "*Product*" under and subject to the terms of the Agreement.

Financial Provisions

Pre-Licensing Milestone Event Payment. To compensate Ionis for the Pre-Licensing Milestone Event described in Section 6.3, JBI shall pay $5,000,000 to Ionis within forty-five (45) days following the First Amendment Effective Date.

License Fee. Following receipt by JBI of a Development Candidate Data Package detailing that the Development Candidate criteria have been met for **[***]** delivery of a JBI **[***]** Development Candidate, JBI will select a JBI **[***]** Development Candidate which will trigger the Option provisions of Article 3 and License Fee under Section 6.4. Notwithstanding, the terms of Sections 3.1 and 3.2, the Option Deadline for JBI to provide Ionis with written notice of its intent to exercise its Option for the JBI **[***]** Development Candidate shall be on or before **[***]**, and JBI shall pay the Option Fee described in Section 6.4 no later than the 45th day following JBI's notice of its intent to exercise such Option.

Post-Licensing Milestone Event Payments. The following Post-Licensing Milestone Event payments described in Table 2 of Section 6.5 are amended as follows solely with respect to the JBI **[***]** Development Candidate:

	Post-Licensing Milestone Event	**Milestone Event Payment**
i)	**[***]**	$**[***]**; and
ii)	**[***]**	$**[***]**

*_*_*_*_*_*

Except as otherwise expressly provided herein, the Agreement shall remain in full force and effect without any amendments or modifications. This First Amendment may be executed in separate counterparts, each of which, whether delivered by electronic mail, or otherwise is deemed to be an original, and all of which taken together shall constitute one and the same instrument. This First Amendment shall be effective as of the First Amendment Effective Date. If the above reflects your understanding of the rights and obligations of the Parties under the Agreement, please acknowledge your agreement of the foregoing by executing the countersignature below.

Very truly yours,

/s/ Austin Clayton
Austin Clayton
Corporate Secretary
Janssen Biotech, Inc.

AGREED & ACCEPTED:

/s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Chief Operating Officer
Date: December 21, 2016

Ionis Pharmaceuticals, Inc.

EXHIBIT 10.61

IONIS PHARMACEUTICALS, INC.

THIRD AMENDED AND RESTATED
STRATEGIC ADVISORY SERVICES AGREEMENT (*"SUMMARY PAGE"*)

This Third Amended and Restated Strategic Advisory Services Agreement is entered into by and between Lyme Pinnacle Consulting Inc., for the services of B. Lynne Parshall, and is made effective as of February 22, 2021, and amends and restates the Strategic Advisory Service Agreement dated January 15, 2018, as amended on March 22, 2019 and January 9, 2020, by and between B. Lynne Parshall and Ionis Pharmaceuticals, Inc. ("***Ionis***").

Date of Third Amended and Restated Strategic Advisory Services Agreement: ("***Agreement***")	February 22, 2021 ("***3rd A&R Effective Date***").
Name of Strategic Advisor:	B. Lynne Parshall (hereinafter "***Strategic Advisor***").
Scope of Strategic Advisory Services:	Provide advisory services to Ionis on projects as directed by the CEO.
Duration of Strategic Advisory Services (the "***Strategic Advisory Period***"):	Commencing January 1, 2021 and continuing through December 31, 2021.
Consideration for Strategic Advisory Services:	Annual fee of $600,000 to be paid quarterly.

In addition to such compensation, Ionis will reimburse Strategic Advisor for Ionis directed travel, lodging and related expenses or reasonable rate equivalents for lodging, car and meals that Strategic Advisor incurs in the course of performing Strategic Advisory Services under this Agreement. All such reimbursements will be in accordance with Ionis' travel policy and Strategic Advisor will provide Ionis with reasonably acceptable supporting documentation.

Strategic Advisor agrees to provide Ionis with Strategic Advisory Services on the terms described above and according to the additional terms attached hereto as Exhibit A. In this Agreement references to Ionis will include Ionis' affiliate companies where applicable.

	Lyme Pinnacle Consulting Inc.	**Ionis Pharmaceuticals, Inc.**
By (Signature):	/s/B. Lynne Parshall	/s/Brett Monia
Date:	February 22, 2021	February 22, 2021
Printed Name:	B. Lynne Parshall, for Lyme Pinnacle Consulting Inc.	Brett Monia

Social Security or Employer Tax ID Number to be provided separately via W-9 form or foreign equivalent.

EXHIBIT A

TERMS OF STRATEGIC ADVISORY AGREEMENT

1. Engagement of Services

Strategic Advisor is retained to perform certain services, as needed and requested by Ionis ("***Strategic Advisory Services***"). Strategic Advisor will perform such Strategic Advisory Services to the best of Strategic Advisor's talent and ability.

2. Compensation

(a) As full and complete compensation for Strategic Advisory Services and for the discharge of all of Strategic Advisor's obligations hereunder, Ionis will pay Strategic Advisor at the annual rate of $600,000 to be paid quarterly. Strategic Advisor will submit reimbursable expenses to Ionis electronically, and Ionis, upon its approval, will pay all undisputed fees and expenses within 30 days after Ionis' receipt of the reimbursement request.

(b) *Ionis Stock Awards:*

(i) Since you transitioned seamlessly from an Ionis employee to a nonemployee director, the stock options and RSUs you received for your previous service as an Ionis employee will continue to vest so long as your Continuous Service (as defined in the applicable equity plan) continues.

(ii) Once you are no longer serving on the Ionis board and no longer providing Strategic Advisory Services, to the extent permitted by the terms of the applicable stock option agreement, your vested stock options will not terminate until the earlier of 18 months following your retirement or the expiration of the original term of such stock option.

(iii) For the 18 months following the end of your Ionis board of directors services, if you are eligible for continued health coverage under COBRA, Ionis will pay your COBRA premium payments sufficient to continue your coverage at your then current level, or if COBRA is not available, Ionis will pay you an amount equal to the cost of comparable replacement coverage.

(c) While you are providing Strategic Advisory Services, Ionis will make an appropriate level of administrative and technical personnel available to facilitate your performance of Advisory Services at no cost to you, including, without limitation IT support and access to Ionis' electronic calendar and IT systems that are necessary to perform your duties.

3. Independent Contractor

Strategic Advisor is an independent contractor and not an employee of Ionis. Strategic Advisor has no authority to obligate Ionis by contract or otherwise. Strategic Advisor will not be eligible for any employee benefits. Taxes will be the sole responsibility of Strategic Advisor.

4. Additional Activities

(a) Strategic Advisor agrees that during the Strategic Advisory Period and for one year thereafter, Strategic Advisor will not attempt to induce any employee or employees of Ionis to terminate their employment with, or otherwise cease their relationship with Ionis.

(b) Strategic Advisor acknowledges that Ionis has developed, through an extensive acquisition process, valuable information regarding actual or prospective partners, licensors, licensees, clients, customers and accounts of Ionis ("***Trade Secret Information***"). Strategic Advisor acknowledges that Strategic Advisor's use of such Trade Secret Information after the termination of the Strategic Advisory Period would cause Ionis irreparable harm. Therefore, Strategic Advisor also agrees that Strategic Advisor will not utilize any Trade Secret Information to solicit the business relationship or patronage of any of the actual or prospective partners, licensors, licensees, clients, customers or accounts of Ionis.

(c) The restrictions set forth in this Section 4 are considered by the parties to be reasonable for the purposes of protecting Ionis' business. However, if any such restriction is found by a court of competent jurisdiction to be unenforceable because it extends for too long a period of time or over too great a range of activities or in too broad a geographic area, it will be interpreted to extend only over the maximum period of time, range of activities or geographic areas as to which it may be enforceable.

5. Confidential Information

(a) Ionis possesses confidential information that has been created, discovered, developed by, or otherwise become known to Ionis (including, without limitation, information created, discovered, developed or made known by Strategic Advisor arising from the Strategic Advisory Services).

(i) All such information is hereinafter referred to as "***Confidential Information***." By way of illustration, but not limitation, Confidential Information includes: (A) inventions, developments, designs, improvements, trade secrets, ideas, formulas, source and object codes, programs, other works of authorship, organisms, plasmids, expression vectors, know-how, processes, cell lines, discoveries, techniques, data and documentation systems (hereinafter collectively referred to as "***Inventions***"); and (B) information regarding plans for research, development, new products, clinical data, pre-clinical product data, clinical trial patient data, marketing and selling, business plans, budgets and unpublished financial statements, licenses, prices and costs, as well as information regarding the skills and compensation of employees of Ionis.

(ii) All Confidential Information will be the sole property of Ionis and its assigns, and Ionis and its assigns will be the sole owner of all patents, copyrights and other rights in connection with such Confidential Information. At all times, both during the term of this Agreement and for five years after its termination, Strategic Advisor will keep in confidence and trust all Confidential Information and will not use, disclose, lecture upon or publish any Confidential Information or anything related to such information without Ionis' prior written consent. Any permitted disclosures will be made in strict compliance with the Ionis publication and presentation clearance policy.

(b) Strategic Advisor also understands that Ionis has received and in the future, will receive valuable information from third parties that is confidential or proprietary ("***Third-Party Information***") subject to a duty on the part of Ionis to maintain the confidentiality of such information and to use it only for certain limited purposes. During the term of this Agreement and for five years thereafter, Strategic Advisor will hold Third-Party Information in the strictest confidence and will not disclose or use Third-Party Information except as permitted by the agreement between Ionis and such third party, unless expressly authorized to act otherwise by an officer of Ionis in writing. Any permitted disclosures will be made in strict compliance with Ionis publication and presentation clearance policy.

(c) The obligations of Section 5 will not apply to information that Strategic Advisor can establish by written records: (i) was known by Strategic Advisor prior to the receipt of Confidential Information; (ii) was disclosed to Strategic Advisor by a third party having the right to do so; (iii) was, or subsequently became, in the public domain through no fault of Strategic Advisor, its officers, directors, affiliates employees or agents; (iv) was independently developed by Strategic Advisor without use of Confidential Information; or (v) was disclosed by Strategic Advisor pursuant to any judicial, governmental or stock exchange request, requirement or order, so long as Strategic Advisor provided Ionis with sufficient prior notice in order to allow Ionis to contest such request, requirement or order.

6. Inventions

In the course of performing Strategic Advisory Services for Ionis, Strategic Advisor may develop new ideas or Inventions or make other contributions of value to Ionis.

(a) Strategic Advisor hereby assigns to Ionis Strategic Advisor's entire right, title and interest in and to any and all Inventions (and all patent rights, copyrights, and all other rights in connection therewith, hereinafter referred to as "***Proprietary Rights***") whether or not patentable or registrable under patent, copyright or similar statutes, made or conceived of or reduced to practice or learned by Strategic Advisor, either alone or jointly with others, as a result of performing Strategic Advisory Services hereunder. All Inventions assigned to Ionis pursuant to this section will be known as "***Company Inventions***". Strategic Advisor agrees that all Proprietary Rights and Company Inventions are Ionis' sole property. Strategic Advisor agrees, upon request, to execute, verify and deliver assignments of such Proprietary Rights to Ionis or its designee. Strategic Advisor understands that, to the extent this Agreement will be construed in accordance with the laws of any state which precludes a requirement in an agreement to assign certain classes of inventions made by an individual acting as a Strategic Advisor, this section will be interpreted not to apply to any inventions that a court rules and/or Ionis agrees falls within such classes.

(b) Strategic Advisor further agrees to assist Ionis in every proper way to obtain, from time to time, and to enforce United States and foreign Proprietary Rights relating to Company Inventions in any and all countries. To that end Strategic Advisor will execute, verify and deliver such documents and perform such other acts (including appearances as a witness) as Ionis may reasonably request for use in applying for, obtaining, sustaining and enforcing such Proprietary Rights relating to Company Inventions. Strategic Advisor's obligation to assist Ionis in obtaining and enforcing Proprietary Rights relating to Company Inventions in any and all countries will continue beyond the termination of this Agreement, but Ionis will compensate Strategic Advisor at a reasonable rate after such termination for the time actually spent by Strategic Advisor at Ionis' request in connection with such assistance. If Ionis is unable, after reasonable effort, to secure Strategic Advisor's signature on any document needed to apply for or prosecute any Proprietary Rights relating to a Company Invention, Strategic Advisor hereby irrevocably designates and appoints Ionis and its duly authorized officers and agents as her agent and attorney in fact, to act for and on Strategic Advisor's behalf to execute, verify and file any such applications and to do all other lawfully permitted acts to further the prosecution and issuance of any such Proprietary Rights with the same legal force and effect as if executed by Strategic Advisor.

(c) During the term of this Agreement, Strategic Advisor will promptly disclose to Ionis, or any persons designated by it, fully and in writing and will hold in trust for the sole right and benefit of Ionis any and all Company Inventions, whether or not patentable or protectable by copyright. At the time of each such disclosure, Strategic Advisor will advise Ionis in writing of any Inventions that Strategic Advisor believes are not subject to the assignment provisions of Section 6(a) above, and Strategic Advisor will at that time provide to Ionis in writing all evidence necessary to substantiate that belief. Strategic Advisor will not be obligated to disclose information received by Strategic Advisor from others under a contract of confidentiality. In addition, after termination of this Agreement, Strategic Advisor will disclose to Ionis all patent applications filed by Strategic Advisor relating to any Company Inventions or relating to any work performed by Strategic Advisor on behalf of Ionis.

7. Previous Strategic Advisory Relationships

Strategic Advisor represents that Strategic Advisor's performance of Strategic Advisory Services, as well as Strategic Advisor's performance of the rest of Strategic Advisor's obligations under the terms of this Agreement, will not breach any agreement to keep in confidence any proprietary information acquired by Strategic Advisor in confidence or in trust from another entity prior to the date of this Agreement. Strategic Advisor agrees not to bring to Ionis or to use in the performance of Strategic Advisory Services for Ionis any materials or documents of a present or former employer or client of Strategic Advisor, or any materials or documents obtained by Strategic Advisor under a confidentiality agreement imposed by reason of another of Strategic Advisor's Strategic Advisory relationships, unless such materials or documents are generally available to the public or Strategic Advisor has authorization from such present or former employer or client for the possession and unrestricted use of such materials.

8. Termination; Survival

(a) The term of this Agreement will begin on January 15, 2018 and will end when terminated by either Ionis or Strategic Advisor. Ionis may terminate this Agreement at any time for any reason by providing Strategic Advisor at least 90 days advance written notice. Strategic Advisor may terminate this Agreement at any time for any reason by providing Ionis at least 90 days advance written notice; *provided*, once Strategic Advisor delivers such a termination notice, Ionis may elect to accelerate the effective date of such termination. Upon any termination, Ionis will pay Strategic Advisor for any Strategic Advisory Services appropriately rendered and for any out of pocket expenses reasonably incurred on behalf of Ionis, up to and including the termination date.

(b) Sections 2(b)(ii) and 2(b)(iii), 9 and 10, will survive termination of this Agreement. In addition, upon expiration or termination of this Agreement, each party will be released from all obligations and liabilities to the other occurring or arising after the date of such expiration or termination, except that any termination or expiration of this Agreement will not relieve Strategic Advisor of Strategic Advisor's obligations under Sections 4, 5, 6, 7, 9, 10 and 11 hereof, nor will any such expiration or termination relieve Strategic Advisor or Ionis from any liability arising from any breach of this Agreement. Upon expiration or termination of this Agreement for any reason whatsoever, Strategic Advisor will promptly surrender and deliver to Ionis any and all notes, business records, memoranda, specifications, devices, formulas, molecules, cells, storage media, including calculations, sequences, data and other materials of any nature pertaining to Strategic Advisory Services for Ionis, as well as any documents or data of any description (or any reproduction of any documents or data) containing or pertaining to any Trade Secret Information, Ionis' Confidential Information or Third Party Information.

9. Arbitration

(a) Ionis and Strategic Advisor agree to resolve by arbitration all disputes, claims or controversies ("***Claims***"), past, present or future, whether or not arising out of this Agreement or its termination, that Ionis may have against Strategic Advisor or that Strategic Advisor may have against any of the following (i) Ionis; (ii) Ionis officers, directors; employees or agents; (iii) Ionis' subsidiary or affiliated entities, joint ventures, or joint employers; (iv) Ionis' benefit plans or the plans' sponsors, fiduciaries, administrators, affiliates and agents; and/or (v) all successors and assigns of any of the foregoing. The Claims covered by this Agreement include all disputes that Ionis or Strategic Advisor could otherwise pursue in state or federal court including, but not limited to, Claims based on any state, federal, or local statute, regulation or ordinance (including Claims for discrimination, retaliation, harassment, unpaid wages or violation of state or federal wage and hour laws), as well as common law Claims (including Claims for breach of contract, breach of the implied covenant of good faith and fair dealing, wrongful discharge, defamation, misrepresentation, fraud, or infliction of emotional distress). Ionis and Strategic Advisor anticipates that this Section 9 provides the benefits of a speedy, less formal, impartial, final and binding dispute resolution procedure.

(b) To the maximum extent permitted by law, Strategic Advisor hereby waives any right to bring on behalf of persons other than Strategic Advisor, or to otherwise participate with other persons in, any class, collective or representative action (i.e. a type of lawsuit in which one or several persons sue on behalf of a larger group of persons).

(c) The arbitration will be conducted by a single neutral arbitrator in accordance with the then- current Commercial Arbitration and Mediation Procedures of the American Arbitration Association ("***AAA***"). The arbitration will take place in San Diego, California. Ionis will pay the arbitrator's fee and will bear all administrative charges by AAA. All parties will be entitled to engage in reasonable pre-hearing discovery to obtain information to prosecute or defend the asserted claims. Any disputes between the parties regarding the nature or scope of discovery will be decided by the arbitrator. The arbitrator will hear and issue a written ruling upon any dispositive motions brought by either party, including but not limited to, motions for summary judgment or summary adjudication of issues. After the hearing, the arbitrator will issue a written decision setting forth the award, if any, and explaining the basis therefore. The arbitrator will have the power to award any type of relief that would be available in court. The arbitrator's award will be final and binding upon the parties and may be entered as a judgment in any court of competent jurisdiction. If there is conflict in the arbitration procedures set forth in this Agreement and the AAA rules specified above, the AAA rules will control. Notwithstanding the foregoing, and regardless of what is provided by the AAA rules, the arbitrator will not have authority or jurisdiction to consolidate claims of different individuals or entities into one proceeding, nor will the arbitrator have authority or jurisdiction to hear the arbitration as a class action. As noted above, Strategic Advisor has agreed to waive any right to bring any class, collective or representative action. To the extent that the class, collective or representative action waiver described above is not enforceable, the issue of whether to certify any alleged or putative class for a class action proceeding must be decided by a court of competent jurisdiction. The arbitrator will not have authority or jurisdiction to decide class certification, collective or representative action issues. Until any class certification, collective, or representative action issues are decided by the court, all arbitration proceedings will be stayed, and the arbitrator will take no action with respect to the matter. However, once any issues regarding class certification, collective, or representative action have been decided by the court, the arbitrator will have authority to decide the substantive claims.

10. Indemnification

(a) Ionis will indemnify, defend and hold Strategic Advisor harmless against any and all losses, costs, expenses and damages (including reasonable attorney's fees) ("Loss(es)") incurred as a result of any third party claims, suits, actions, demands or proceedings resulting or arising from the performance of Strategic Advisory Services as specifically directed by Ionis in accordance with the Agreement to the extent such Loss(es) are not the result of Strategic Advisor's gross negligence, intentional misconduct or material breach of this Agreement.

(b) Ionis' agreement to indemnify, defend and hold Strategic Advisor harmless is conditioned upon the Strategic Advisor (i) providing written notice to Ionis of any claim, demand or action arising out of the indemnified activities within thirty (30) days after Strategic Advisor has knowledge of such claim, demand or action, *provided* that the failure to so notify Ionis shall not relieve Ionis of its obligations hereunder except to the extent such failure shall have actually materially prejudiced Ionis; (ii) permitting Ionis to assume full responsibility to investigate, prepare for and defend against any such claim or demand; (iii) assisting Ionis, at Ionis' reasonable expense, in the investigation of, preparation of and defense of any such claim or demand; (iv) undertaking reasonable steps to mitigate any loss, damage or expense with respect to the applicable claim or demand; and (v) not settling such claim or demand without Ionis' prior written consent.

(c) Ionis will endeavor to include Strategic Advisor as a covered attorney on its insurance policy for attorneys who advise Ionis.

11. Miscellaneous

(a) The rights and liabilities of the parties hereto will bind and inure to the benefit of their respective successors, heirs, executors and administrators, as the case may be; *provided that*, as Ionis has specifically contracted for Strategic Advisor's services, Strategic Advisor may not assign or delegate Strategic Advisor's obligations under this Agreement either in whole or in part without Ionis' prior written consent.

(b) Because Strategic Advisor's services are personal and unique and because Strategic Advisor has access to and become acquainted with Ionis' Confidential Information, the parties agree that in the event of a threatened or actual material breach of this Agreement by Strategic Advisor injunctive relief would be appropriate. As such, Ionis has the right to enforce this Agreement and any of its provisions by injunction, specific performance or other equitable relief without prejudice to any other rights and remedies that Ionis may have for a breach of this Agreement.

(c) This Agreement will be governed by and construed according to the laws of the State of California as such laws are applied to contracts entered into and performed entirely within such State. If any provision of this Agreement is held to be or becomes invalid, illegal or unenforceable, such provision will be validly reformed to approximate as nearly as possible the intent of the parties and the remainder of this Agreement will not be affected thereby and will remain valid and enforceable to the greatest extent permitted by law.

(d) This Agreement, and all other documents mentioned herein, constitute the final, exclusive and complete understanding and agreement of the parties hereto and supersedes all prior understandings and agreements. Any waiver, modification or amendment of any provision of this Agreement will be effective only if in writing and signed by the parties hereto.

(e) Any notices required or permitted hereunder will be given to the appropriate party at the address specified on the Summary Page or at such other address as the party will specify in writing. Such notice will be deemed given upon personal delivery to the appropriate address, or by facsimile transmission (receipt verified and with confirmation copy followed by another permitted method), sent by express courier service, or, if sent by certified or registered mail, three (3) days after the date of mailing.

EXHIBIT 10.79

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 "[***]".

AMENDMENT NO. 3

This Amendment No. 3 (the "***Amendment***") to the Strategic Collaboration Agreement dated July 31, 2015, as previously amended by Amendment No. 1 dated October 18, 2018, and Amendment No. 2 dated April 30, 2020 (the "***Agreement***"), is made by and between

(1) ASTRAZENECA AB, a company incorporated in Sweden under no. 556011-7482 with its registered office at SE-151 85 Södertälje, Sweden ("***AstraZeneca***") and

(2) IONIS PHARMACEUTICALS, INC., a Delaware corporation, (formally known as Isis Pharmaceuticals, Inc.) having its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010 ("***Ionis***"),

and is made effective as of December 17, 2020 (the "***Amendment Effective Date***").

Recitals

WHEREAS, the Parties desire to amend the Agreement to extend the Disease Research Term.

NOW, THEREFORE, in consideration of the mutual covenants contained in this Amendment, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, agree as follows:

Agreement

1. **Definitions**

Any capitalized term not separately defined in this Amendment shall have the meaning ascribed to it in the Agreement.

2. **Modifications**

Section 1.3.2 of the Agreement is hereby deleted in its entirety and replaced with the following:

"1.3.2. **Disease Research Term**. The term for the conduct of the Disease Research Program will begin on the Effective Date and will end on the [***] anniversary of the Effective Date (the "***Disease Research Term***")."

3. **Amendment Effective Date**

This Amendment shall become effective on the Amendment Effective Date.

4. **Entire Agreement**

The Agreement together with this Amendment constitutes the entire agreement between the Parties with respect to the subject matter of the Agreement. The Agreement together with this Amendment supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreement. Each Party confirms that it is not relying on any representations, warranties, or covenants of the other Party except as specifically set out in the Agreement or this Amendment. Nothing in this Amendment is intended to limit or exclude any liability or fraud. The Parties hereby agree that subject to the modifications specifically stated in this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect.

Execution

THIS AMENDMENT IS EXECUTED by the authorized representatives of the Parties as of the date first written above.

ASTRAZENECA AB (publ.)		**IONIS PHARMACEUTICALS, INC.**	
Signature:	/s/ Regina Fritsche Danielson	Signature:	/s/ Brett Monia
Name:	Regina Fritsche Danielson	Name:	Brett Monia
Title:	SVP and Head of Research and Early Development, Cardiovascular, Renal and Metabolism	Title:	CEO

Execution Copy

EXHIBIT 10.80

IONIS PHARMACEUTICALS, INC.
ADVISORY SERVICES AGREEMENT
(*"SUMMARY PAGE"*)

Date of Advisory Services Agreement: ("***Agreement***")	December 17, 2020 ("***Effective Date***").
Name of Advisor:	Stanley T. Crooke (hereinafter "***Advisor***").
Scope of Advisory Services:	As set forth on Schedule A attached hereto.
Duration of Advisory Services (the "***Advisory Period***"):	An initial term beginning immediately following the June 2, 2021 Annual Stockholders Meeting and ending on June 30, 2023 unless extended or terminated in accordance with Section 8 of Exhibit A below.
Consideration for Advisory Services:	As set forth on Schedule B attached hereto.
Time Provided by Advisor:	As set forth on Schedule A attached hereto.

In addition to such compensation, Ionis Pharmaceuticals, Inc. ("***Ionis***") will reimburse Advisor for Ionis approved travel and other out-of-pocket costs reasonably incurred in the course of performing Advisory Services under this Agreement as further described on Schedule B attached hereto. Advisor shall be permitted to travel at first-class level on commercial carriers.

Advisor agrees to provide Ionis with Advisory Services on the terms described above and according to the additional terms attached hereto as Exhibit A. In this Agreement references to Ionis, including but not limited to Sections 3-6 of Exhibit A, will include Ionis' affiliate companies where applicable.

	Advisor	**Ionis Pharmaceuticals, Inc.**
By (Signature):	/s/ Stanley T. Crooke	/s/ Joseph H. Wender
Printed Name:	Stanley T. Crooke	Joseph H. Wender - Chair of Nominating & Governance Committee
By (Signature):	NA	/s/ Spencer R. Berthelsen
Printed Name:	NA	Spencer R. Berthelsen – Chair of Compensation Committee
Address:	Provided Separately	2855 Gazelle Court, Carlsbad, CA 92010
Telephone:	Provided Separately	760-931-9200
Fax:	Provided Separately	760-603-3820
e-mail:	Provided Separately	

Social Security or Employer Tax ID Number to be provided separately via W-9 form or foreign equivalent.

EXHIBIT A

TERMS OF ADVISORY AGREEMENT

1. **Engagement of Services; Transition From Executive Chairman to Advisor; Press Release**

Advisor is retained to perform certain services during the Advisory Period, as needed and requested by Ionis, which services are specifically described on Schedule A attached hereto ("***Advisory Services***"). Advisor will perform such Advisory Services to the best of Advisor's talent and ability.

Advisor hereby voluntarily retires and resigns from his position as an employee and member of the Board of Directors of Ionis, which resignation will take effect immediately following the June 2, 2021 Annual Stockholders Meeting

Promptly following the Effective Date of this Agreement, Ionis will announce Advisor's retirement and transition to his role as Advisor pursuant to a press release drafted by Ionis and approved by Advisor (such approval not to be unreasonably withheld, conditioned or delayed).

2. **Compensation**

As full and complete compensation for Advisory Services and for the discharge of all of Advisor's obligations hereunder, Ionis will pay Advisor at the rate set forth on Schedule B attached hereto and provide the other consideration set forth on Schedule B. Advisor will invoice Ionis on a quarterly basis for Advisor fees and reimbursable expenses, and Ionis, upon its approval, will pay all undisputed fees and expenses within 30 days after Ionis' receipt of the invoice.

3. **Independent Contractor**

Advisor is an independent contractor and not an employee of Ionis. Advisor has no authority to obligate Ionis by contract or otherwise. Taxes will be the sole responsibility of Advisor.

4. **Additional Activities**

(a) Advisor agrees that during the Advisory Period and for one year thereafter, Advisor will not attempt to induce any employee or employees of Ionis to terminate their employment with, or otherwise cease their relationship with Ionis.

(b) Advisor acknowledges that Ionis has developed, through an extensive acquisition process, valuable information regarding actual or prospective partners, licensors, licensees, clients, customers and accounts of Ionis ("***Trade Secret Information***"). Advisor acknowledges that Advisor's use of such Trade Secret Information after the termination of the Advisory Period would cause Ionis irreparable harm. Therefore, Advisor also agrees that Advisor will not utilize any Trade Secret Information to solicit the business relationship or patronage of any of the actual or prospective partners, licensors, licensees, clients, customers or accounts of Ionis.

(c) The restrictions set forth in this Section 4 are considered by the parties to be reasonable for the purposes of protecting Ionis' business. However, if any such restriction is found by a court of competent jurisdiction to be unenforceable because it extends for too long a period of time or over too great a range of activities or in too broad a geographic area, it will be interpreted to extend only over the maximum period of time, range of activities or geographic areas as to which it may be enforceable.

5. Confidential Information; No disparagement

(a) Ionis possesses confidential information that has been created, discovered, developed by, or otherwise become known to Ionis (including, without limitation, information which is created, discovered, developed or made known by Advisor arising from the Advisory Services).

(i) All such information is hereinafter referred to as "***Confidential Information***." By way of illustration, but not limitation, Confidential Information includes: (A) inventions, developments, designs, improvements, trade secrets, ideas, formulas, source and object codes, programs, other works of authorship, organisms, plasmids, expression vectors, know-how, processes, cell lines, discoveries, techniques, data and documentation systems (hereinafter collectively referred to as "***Inventions***"); and (B) information regarding plans for research, development, new products, clinical data, pre-clinical product data, clinical trial patient data, marketing and selling, business plans, budgets and unpublished financial statements, licenses, prices and costs, as well as information regarding the skills and compensation of employees of Ionis.

(ii) All Confidential Information will be the sole property of Ionis and its assigns, and Ionis and its assigns will be the sole owner of all patents, copyrights and other rights in connection with such Confidential Information. At all times, both during the term of this Agreement and for five years after its termination, Advisor will keep in confidence and trust all Confidential Information and will not use, disclose, lecture upon or publish any Confidential Information or anything related to such information without Ionis' prior written consent or as otherwise reasonably necessary in furtherance of Advisor performing the Advisory Services. Any permitted disclosures will be made in strict compliance with the Ionis publication and presentation clearance policy.

(b) Advisor also understands that Ionis has received and in the future, will receive valuable information from third parties that is confidential or proprietary ("***Third-Party Information***") subject to a duty on the part of Ionis to maintain the confidentiality of such information and to use it only for certain limited purposes. During the term of this Agreement and for five years thereafter, Advisor will hold Third-Party Information in the strictest confidence and will not disclose or use Third-Party Information except as permitted by the agreement between Ionis and such third party, unless expressly authorized to act otherwise by an officer of Ionis in writing or as otherwise reasonably necessary in furtherance of Advisor performing the Advisory Services. Any permitted disclosures will be made in strict compliance with Ionis publication and presentation clearance policy.

(c) The obligations of Section 5 will not apply to information that Advisor can establish by written records: (i) was known by Advisor prior to the receipt of Confidential Information; (ii) was disclosed to Advisor by a third party having the right to do so; (iii) was, or subsequently became, in the public domain through no fault of Advisor, its officers, directors, affiliates employees or agents; (iv) was independently developed by Advisor without use of Confidential Information; or (v) was disclosed by Advisor pursuant to any judicial, governmental or stock exchange request, requirement or order, so long as Advisor, if legally permitted, provided Ionis with sufficient prior notice in order to allow Ionis to contest such request, requirement or order. Advisor may also disclose Confidential Information to his legal counsel and financial advisor and as reasonably necessary pursuant to any litigation between Advisor and Ionis or any of its affiliates.

(d) Ionis agrees that its executive officers and the current members of its Board of Directors and the heads of the Investor Relations and Corporate Communication Departments) will not disparage or knowingly make false or defamatory statements regarding Advisor in any manner whatsoever (including through the use of any social networking sites, blogs, forums or any similar medium, including in response to inquiries from other users of such medium) whether directly or indirectly through a third party. Advisor agrees that he will not disparage or knowingly make false or defamatory statements about Ionis, or its directors, officers, or affiliates in any manner whatsoever (including through the use of any social networking sites, blogs, forums or any similar medium, including in response to inquiries from other users of such medium) whether directly or indirectly through a third party. This Section shall not apply to communications (i) required by law, court order or subpoena, (ii) that are otherwise privileged as a matter of law, (iii) that are made to correct inaccurate or misleading statements made about Advisor or Ionis, as applicable or (iv) that are reasonably appropriate to be made in connection with any litigation between Advisor and Ionis or its affiliates. Advisor's and Ionis' non-disparagement obligations under this Section do not interfere with or restrict his or its ability to communicate with any federal, state, or local agency, including any with which a charge has been filed.

6. **Inventions**

In the course of performing Advisory Services for Ionis, Advisor may develop new ideas or Inventions or make other contributions of value to Ionis.

(a) Advisor hereby assigns to Ionis Advisor's entire right, title and interest in and to any and all Inventions (and all patent rights, copyrights, and all other rights in connection therewith, hereinafter referred to as "***Proprietary Rights***") whether or not patentable or registrable under patent, copyright or similar statutes, made or conceived of or reduced to practice or learned by Advisor, either alone or jointly with others, as a result of performing Advisory Services hereunder. All Inventions assigned to Ionis pursuant to this section will be known as "***Company Inventions***". Advisor agrees that all Proprietary Rights and Company Inventions are Ionis' sole property. Advisor agrees, upon request, to execute, verify and deliver assignments of such Proprietary Rights to Ionis or its designee. Advisor understands that, to the extent this Agreement will be construed in accordance with the laws of any state which precludes a requirement in an agreement to assign certain classes of inventions made by an individual acting as an Advisor, this section will be interpreted not to apply to any inventions that a court rules and/or Ionis agrees falls within such classes.

(b) Advisor further agrees to assist Ionis in every proper way to obtain, from time to time, and to enforce United States and foreign Proprietary Rights relating to Company Inventions in any and all countries. To that end Advisor will execute, verify and deliver such documents and perform such other acts (including appearances as a witness) as Ionis may reasonably request for use in applying for, obtaining, sustaining and enforcing such Proprietary Rights relating to Company Inventions. Advisor's obligation to assist Ionis in obtaining and enforcing Proprietary Rights relating to Company Inventions in any and all countries will continue beyond the termination of this Agreement, but Ionis will compensate Advisor at a reasonable rate after such termination for the time actually spent by Advisor at Ionis' request in connection with such assistance. If Ionis is unable, after reasonable effort, to secure Advisor's signature on any document needed to apply for or prosecute any Proprietary Rights relating to a Company Invention, Advisor hereby irrevocably designates and appoints Ionis and its duly authorized officers and agents as her agent and attorney in fact, to act for and on Advisor's behalf to execute, verify and file any such applications and to do all other lawfully permitted acts to further the prosecution and issuance of any such Proprietary Rights with the same legal force and effect as if executed by Advisor.

(d) During the term of this Agreement, Advisor will promptly disclose to Ionis, or any persons designated by it, fully and in writing and will hold in trust for the sole right and benefit of Ionis any and all Company Inventions, whether or not patentable or protectable by copyright. At the time of each such disclosure, Advisor will advise Ionis in writing of any Inventions that Advisor believes are not subject to the assignment provisions of Section 6(a) above, and Advisor will at that time provide to Ionis in writing all evidence necessary to substantiate that belief. Advisor will not be obligated to disclose information received by Advisor from others under a contract of confidentiality. In addition, after termination of this Agreement, Advisor will disclose to Ionis all patent applications filed by Advisor relating to any Company Inventions or relating to any work performed by Advisor on behalf of Ionis.

7. Previous Advisory Relationships

Advisor represents that Advisor's performance of Advisory Services, as well as Advisor's performance of the rest of Advisor's obligations under the terms of this Agreement, will not breach any agreement to keep in confidence any proprietary information acquired by Advisor in confidence or in trust from another entity prior to the date of this Agreement. Advisor agrees not to bring to Ionis or to use in the performance of Advisory Services for Ionis any materials or documents of a present or former employer or client of Advisor, or any materials or documents obtained by Advisor under a confidentiality agreement imposed by reason of another of Advisor's Advisory relationships, unless such materials or documents are generally available to the public or Advisor has authorization from such present or former employer or client for the possession and unrestricted use of such materials.

8. **Termination; Survival**

(a) This Agreement will become effective on the Effective Date and will end on June 30, 2023 unless the parties mutually agree by written amendment to extend this Agreement. If Ionis believes that Advisor is in material breach of this Agreement, then Ionis may deliver notice of such material breach to Advisor. If the breach is curable, Advisor will have 60 days to cure such breach. If Advisor fails to cure such breach within the 60 day period, or if the breach is not subject to cure, Ionis may terminate this Agreement by providing written notice to Advisor. Without limiting the foregoing, the intentional material breach by Advisor of Section 5 of this Agreement constitutes a material breach of this Agreement.

(b) The last sentence of the second paragraph of Schedule B and the last paragraph of Schedule B will survive termination of this Agreement. In addition, except as referenced in the immediately preceding sentence, upon expiration or termination of this Agreement, each party will be released from all obligations and liabilities to the other occurring or arising after the date of such expiration or termination, except that any termination or expiration of this Agreement will not relieve Advisor of Advisor's obligations under Sections 4, 5, 6, 7, 9, 10 and 11 hereof, nor will any such expiration or termination relieve Advisor or Ionis from any liability arising from any breach of this Agreement. Upon expiration or termination of this Agreement for any reason whatsoever, Advisor will promptly surrender and deliver to Ionis any and all notes, business records, memoranda, specifications, devices, formulas, molecules, cells, storage media, including calculations, sequences, data and other materials of any nature pertaining to Advisory Services for Ionis, as well as any documents or data of any description (or any reproduction of any documents or data) containing or pertaining to any Trade Secret Information, Ionis' Confidential Information or Third Party Information.

9. **Arbitration**

(a) Ionis and Advisor agree to resolve by arbitration all disputes, claims or controversies ("***Claims***"), past, present or future, whether or not arising out of this Agreement or its termination, that Ionis may have against Advisor or that Advisor may have against any of the following (i) Ionis; (ii) Ionis officers, directors; employees or agents; (iii) Ionis' subsidiary or affiliated entities, joint ventures, or joint employers; (iv) Ionis' benefit plans or the plans' sponsors, fiduciaries, administrators, affiliates and agents; and/or (v) all successors and assigns of any of the foregoing. The Claims covered by this Agreement include all disputes that Ionis or Advisor could otherwise pursue in state or federal court including, but not limited to, Claims based on any state, federal, or local statute, regulation or ordinance (including Claims for discrimination, retaliation, harassment, unpaid wages or violation of state or federal wage and hour laws), as well as common law Claims (including Claims for breach of contract, breach of the implied covenant of good faith and fair dealing, wrongful discharge, defamation, misrepresentation, fraud, or infliction of emotional distress). Ionis and Advisor anticipates that this Section 9 provides the benefits of a speedy, less formal, impartial, final and binding dispute resolution procedure.

(b) To the maximum extent permitted by law, Advisor hereby waives any right to bring on behalf of persons other than Advisor, or to otherwise participate with other persons in, any class, collective or representative action (i.e. a type of lawsuit in which one or several persons sue on behalf of a larger group of persons).

(c) The arbitration will be conducted by a single neutral arbitrator in accordance with the then-current Commercial Arbitration and Mediation Procedures of the American Arbitration Association ("***AAA***"). The arbitration will take place in San Diego, California. Ionis will pay the arbitrator's fee and will bear all administrative charges by AAA. All parties will be entitled to engage in reasonable pre-hearing discovery to obtain information to prosecute or defend the asserted claims. Any disputes between the parties regarding the nature or scope of discovery will be decided by the arbitrator. The arbitrator will hear and issue a written ruling upon any dispositive motions brought by either party, including but not limited to, motions for summary judgment or summary adjudication of issues. After the hearing, the arbitrator will issue a written decision setting forth the award, if any, and explaining the basis therefore. The arbitrator will have the power to award any type of relief that would be available in court. The arbitrator's award will be final and binding upon the parties and may be entered as a judgment in any court of competent jurisdiction. If there is conflict in the arbitration procedures set forth in this Agreement and the AAA rules specified above, the AAA rules will control. Notwithstanding the foregoing, and regardless of what is provided by the AAA rules, the arbitrator will not have authority or jurisdiction to consolidate claims of different individuals or entities into one proceeding, nor will the arbitrator have authority or jurisdiction to hear the arbitration as a class action. As noted above, Advisor has agreed to waive any right to bring any class, collective or representative action. To the extent that the class, collective or representative action waiver described above is not enforceable, the issue of whether to certify any alleged or putative class for a class action proceeding must be decided by a court of competent jurisdiction. The arbitrator will not have authority or jurisdiction to decide class certification, collective or representative action issues. Until any class certification, collective, or representative action issues are decided by the court, all arbitration proceedings will be stayed, and the arbitrator will take no action with respect to the matter. However, once any issues regarding class certification, collective, or representative action have been decided by the court, the arbitrator will have authority to decide the substantive claims.

10. Indemnification; Representations

(a) Ionis will indemnify, defend and hold Advisor harmless against any and all losses, costs, expenses and damages (including advancement of reasonable attorney's fees) (***"Loss(es)"***) incurred as a result of any third party claims, suits, actions, demands or proceedings resulting or arising from the performance of Advisory Services as specifically directed by Ionis in accordance with the Agreement to the extent such Loss(es) are not the result of Advisor's gross negligence, intentional misconduct or material breach of this Agreement.

(b) Ionis' agreement to indemnify, defend and hold Advisor harmless is conditioned upon the Advisor (i) providing written notice to Ionis of any claim, demand or action arising out of the indemnified activities within thirty (30) days after Advisor has knowledge of such claim, demand or action, provided that the failure to so notify Ionis shall not relieve Ionis of its obligations hereunder except to the extent such failure shall have actually materially prejudiced Ionis; (ii) permitting Ionis to assume full responsibility to investigate, prepare for and defend against any such claim or demand; (iii) assisting Ionis, at Ionis' reasonable expense, in the investigation of, preparation of and defense of any such claim or demand; (iv) undertaking reasonable steps to mitigate any loss, damage or expense with respect to the applicable claim or demand; and (v) not settling such claim or demand without Ionis' prior written consent.

(c) Advisor represents and warrants to Ionis that (i) Advisor has complied in all material respects with his fiduciary duties and responsibilities as an officer and member of the board of directors of Ionis and (ii) Advisor is not aware of any set of facts or circumstances that may reasonably give rise to litigation or other legal proceeding between Advisor and Ionis. Ionis represents and warrants to Advisor that Ionis is not aware of any set of facts or circumstances that may reasonably give rise to litigation or other legal proceeding between Ionis and Advisor.

11. Miscellaneous

(a) The rights and liabilities of the parties hereto will bind and inure to the benefit of their respective successors, heirs, executors and administrators, as the case may be; *provided that*, as Ionis has specifically contracted for Advisor's services, Advisor may not assign or delegate Advisor's obligations under this Agreement either in whole or in part without Ionis' prior written consent, and Ionis may not assign Ionis' obligations under this Agreement either in whole or in part without Advisor's prior written consent, other than in connection with a corporate transaction resulting in a sale of Ionis or substantially all of its assets.

(b) Because Advisor's services are personal and unique and because Advisor has access to and become acquainted with Ionis' Confidential Information, the parties agree that in the event of a threatened or actual material breach of this Agreement by Advisor injunctive relief would be appropriate. As such, Ionis has the right to enforce this Agreement and any of its provisions by injunction, specific performance or other equitable relief without prejudice to any other rights and remedies that Ionis may have for a breach of this Agreement.

(c) This Agreement will be governed by and construed according to the laws of the State of California as such laws are applied to contracts entered into and performed entirely within such State. If any provision of this Agreement is held to be or becomes invalid, illegal or unenforceable, such provision will be validly reformed to approximate as nearly as possible the intent of the parties and the remainder of this Agreement will not be affected thereby and will remain valid and enforceable to the greatest extent permitted by law.

(d) This Agreement, and all other documents mentioned herein, constitute the final, exclusive and complete understanding and agreement of the parties hereto and supersedes all prior understandings and agreements; provided the employee proprietary information and invention agreement between Advisor and Ionis will remain in full force and effect. Any waiver, modification or amendment of any provision of this Agreement will be effective only if in writing and signed by the parties hereto.

(e) Any notices required or permitted hereunder will be given to the appropriate party at the address specified on the Summary Page or at such other address as the party will specify in writing. Such notice will be deemed given upon personal delivery to the appropriate address, or by facsimile transmission (receipt verified and with confirmation copy followed by another permitted method), sent by express courier service, or, if sent by certified or registered mail, three (3) days after the date of mailing.

(f) Each party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

[END OF EXHIBIT A]

SCHEDULE A

Advisory Services

As requested by Ionis' CEO or Chairman of the Board of Directors you will provide the following advisory services:

- Participate in and provide advice regarding drug discovery and development decisions (RMC/DMC, advice to teams as requested)
- Participate in advancing the science at Ionis via program reviews, Core antisense research meetings (CAR) and other activities as reasonably requested
- Lead the scientific activities for the Crooke Group (Ionis Dept #260)
- Participate as a key spokesman for Ionis' technology
- Participate as a key spokesman for Ionis when requested by and coordinated with Ionis; provided communications regarding Ionis' management or strategy will be Ionis' sole responsibility.

While you are providing such services, Ionis will provide administrative assistance to you with the same personnel (i.e. Kim Butler) at the same level of service as you received during your tenure as Executive Chairman. If Ms. Butler applies for another position within Ionis for which she is qualified, Ionis will reasonably consider her application for the position. As such, if Ms. Butler's service with Ionis terminates or she voluntarily takes another position within Ionis, Ionis will provide an appropriate level of administrative assistance to you. Ionis will also provide appropriate office space for you and your administrative support when you are on site at Ionis' facilities.

In addition, Ionis will provide an appropriate level of technical personnel available to facilitate your performance of Advisory Services at no cost to you, including, without limitation IT support and access to Ionis' electronic calendar, files and IT systems that are necessary to perform your duties.

SCHEDULE B

Compensation for Advisory Services

For your Advisory services, starting after the June 2021 annual meeting of stockholders, Ionis will pay you at the rate of $100,000 per calendar quarter, payable in accordance with Section 2 of the Agreement. If this agreement is extended past the 2022 – 2023 service year payment for services will be set by mutual written agreement between you and Ionis, based on the expected services for such year

Since you are transitioning seamlessly from an Ionis employee to a consultant, the stock options and RSUs you received for your previous service as an Ionis employee (collectively, ***"Employee Equity Awards"***) will continue to vest so long as your Continuous Service (as defined in the applicable equity plan) continues. For the avoidance of doubt, your Advisory Services shall be treated as Continuous Service. If your Continuous Service terminates during the term of this Agreement or upon the expiration of this Agreement (other than for a termination by Ionis for your material breach of this Agreement), your Employee Equity Awards that are not vested will become immediately vested upon such termination. Upon the closing of a Change in Control of Ionis (as defined in the Amended and Restated Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan), your Employee Equity Awards that are not vested will become immediately vested. Any vested stock options held by Advisor shall continue to remain exercisable while Advisor is providing Continuous Service and the applicable exercise period shall continue following termination of Continuous Service as if such termination were a termination of employment.

From the end of your Ionis board of directors services through June 30, 2023, if you are eligible for continued health coverage under COBRA, Ionis will pay your COBRA premium payments sufficient to continue your coverage at your then current level, or if COBRA is not available, Ionis will pay you on a monthly basis an amount equal to the cost of comparable replacement coverage.

EXHIBIT 10.81

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 "[***]".

December 31, 2020

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142
Attention: Chief Legal Officer
Email: **[***]**@biogen.com

Re: [***] Collaboration Program

Dear Anabella:

Reference is hereby made to that certain New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between Ionis Pharmaceuticals, Inc. ("***Ionis***") and Biogen MA Inc. ("***Biogen***") dated April 19, 2018, as supplemented or amended to date (the "***Agreement***"). Any capitalized terms not defined herein will have the meaning set forth in the Agreement.

WHEREAS, Biogen and Ionis have discussed the use of certain drug delivery technology, including **[***]** (each a "**[***]**") and **[***]** (each, a "**[***]**"), in each case targeting the **[***]**;

WHEREAS, Biogen has identified certain specific **[***]**and specific **[***]**;

WHEREAS, as of the date hereof, the Neurology Target **[***]** is a High Interest Target;

WHEREAS, as of the date hereof, the Parties are pursuing a Collaboration Program consisting of a Strategy directed against **[***]** for **[***]** (such Strategy, the "**[***]** ***Strategy***," and such Collaboration Program, the "**[***]** ***Collaboration Program***"); and

WHEREAS, the Parties desire to (i) designate an alternative Strategy directed to **[***]** pursuant to which the Parties would **[***]** (as defined below) with an **[***]** directed against **[***]** for **[***]** and (ii) designate such Strategy directed to **[***]** as an additional Collaboration Program under the Agreement (such Strategy, the "**[***]** ***Strategy***," and such Collaboration Program, the "**[***]** ***Collaboration Program***").

NOW, THEREFORE, for the promises set forth herein and valuable consideration (the receipt and adequacy of which is hereby acknowledged), solely with respect to **[***]**, the Parties agree to modify the Agreement as follows:

1. **Selection of [***]**. Each **[***]** or **[***]** provided by Biogen to Ionis under this letter agreement or the Agreement and identified by Biogen by sequence will be a "***Biogen* [***]**" or "***Biogen* [***]**," respectively (collectively, the "***Biogen* [***]**"). The Parties will select the final Biogen **[***]** for inclusion in the **[***]** Development Candidate and such selection will be reflected in the minutes of the Neurology JRC or Neurology JDC.

2. **Designation of [***] Collaboration Program; Target Designation Milestone Payment**. The Parties hereby (a) designate the **[***]** Strategy as an alternative Strategy directed to **[***]** and (b) designate the **[***]** Strategy as a Collaboration Program. Notwithstanding any provision to the contrary set forth in the Agreement, the Target Designation Milestone for the **[***]** Strategy will be **[***]**. Such payment will be due and payable no later than **[***]** (**[***]**) Business Days after the date of receipt an invoice therefor from Ionis.

3. **Supply of [***]**. Notwithstanding any provision to the contrary set forth in the Agreement, including Section 1.8.6 (Manufacturing and Supply for Collaboration Programs), before the License Effective Date with respect to the **[***]** Strategy, to the extent necessary, Biogen, at its expense, will supply research-grade **[***]** to Ionis sufficient to (a) support the Research and Development activities under the **[***]** Strategy as set forth in the applicable Development Candidate Identification Plan, and (b) support IND-Enabling Toxicology Studies pursuant to the applicable Toxicology Strategy. Notwithstanding any provision to the contrary set forth in the Agreement, including Section 1.8.4 (IND-Enabling Toxicology Studies), unless the Neurology JDC agrees otherwise, Biogen will conduct and lead, all IND-Enabling Toxicology Studies for all Development Candidates under the **[***]** Collaboration Program, in accordance with the applicable IND-Enabling Toxicology Study design and Toxicology Strategy (that are each approved pursuant to Section 1.8.4 (IND-Enabling Toxicology Studies)) and the other terms of the Agreement.

4. **Materials**. To facilitate the conduct of activities under the **[***]** Collaboration Program or the performance of other activities for such Collaboration Program under the Agreement or this letter agreement, Biogen may provide to Ionis or its Affiliates certain compositions of matter, biological materials, or chemical compounds Controlled by Biogen, including the Biogen **[***]**, for use by Ionis (such materials or compounds and any progeny and derivatives thereof, collectively, "***Materials***"). Except as otherwise set forth in this Agreement, all such Materials will remain the sole property of Biogen, will be used only in the fulfillment of obligations or exercise of rights under the Agreement expressly in accordance with the applicable Neurology Plan or other written agreement by the Parties as to the use thereof, subject to any limitations specified in writing by Biogen in connection with such provision, which restrictions will not further limit Ionis' rights under this letter agreement or the Agreement, will not be used or delivered to or for the benefit of any Third Party without the prior written consent of Biogen (except as expressly permitted under the applicable Neurology Plan), and will not be used in research or testing involving human subjects, unless expressly agreed by Biogen. Without limiting the foregoing, Ionis will not reverse engineer, disassemble, modify, create, or engineer any type of **[***]** from, any Biogen **[***]**, Biogen **[***]**, Biogen **[***]**, or Biogen **[***]** provided to Ionis under the Agreement or this letter agreement. Except as otherwise set forth in the Agreement or in this letter agreement, THE MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT RIGHT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

5. **Interpretation**. Solely with respect to the **[***]** Collaboration Program, Section 1.8.6 (Manufacturing and Supply for Collaboration Programs) and Section 4.8.2(c) (API and Product) of the Agreement are hereby amended as follows:

a. In Section 1.8.6 (Manufacturing and Supply for Collaboration Programs), the terms "ASO" and "API" will be deemed to exclude any **[***]** or **[***]** that is incorporated into any Compound, Development Candidate, or Product; and

b. In Section 4.8.2(c) (API and Product), the terms "bulk Development Candidate," "API," "Clinical Supplies" and "Finished Drug Product" will be deemed to include any ASO that is incorporated into the applicable Compound, Development Candidate or Product, whether alone or in combination with any **[***]** or **[***]**.

6. **Initiation of IND-Enabling Toxicology Study**. There will be **[***]** under Section 6.3 (Milestone Payments for First Initiation of IND-Enabling Toxicology Studies) for the **[***]** Milestone with respect to the **[***]** Collaboration Program.

7. **License Fee**. Notwithstanding any provision to the contrary set forth in the Agreement, including Section 6.4 (License Fee), the Option Fee for the **[***]** Collaboration Program will be $**[***]**.

8. **[***] Post-Option Development Milestone Payments**. If a Product under the **[***]** Collaboration Program is classified as a **[***]** under the Agreement in accordance with Section 6.5 (Collaboration Program Asset Size Determination), then **[***]** the milestone payments under Section 6.7 (Post-Option Development Milestone Payments), Biogen will pay to Ionis the milestone payments as set forth below when a Post-Option Development Milestone Event listed below is first achieved by Biogen, or its Affiliates or Sublicensees for such Product under the **[***]** Collaboration Program:

Post-Option Development Milestone Event	**Milestone Event Payment for the first Product from the [***] Collaboration Program**
[***]	$**[***]**
[***]	$**[***]**
[***]	$**[***]**

9. **[***] Post-Option Development Milestone Payments**. If a Product under the **[***]** Collaboration Program is classified as a **[***]** under the Agreement in accordance with Section 6.5 (Collaboration Program Asset Size Determination), then **[***]** the milestone payments under Section 6.7 (Post-Option Development Milestone Payments), Biogen will pay to Ionis the milestone payments as set forth below when a Post-Option Development Milestone Event listed below is first achieved by Biogen, its Affiliates or Sublicensees for such Product under the **[***]** Collaboration Program:

Post-Option Development Milestone Event	Milestone Event Payment for the first Product from the [***] Collaboration Program
[***]	$[***]
[***]	$[***]
[***]	$[***]

10. **Ownership of [***] and [***]**. Notwithstanding any provision to the contrary set forth in the Agreement, the Parties agree that:

a. as between the Parties, Biogen is the sole owner of all rights, title, and interests in and to the Biogen **[***]**, and the Biogen **[***]** will be considered Biogen **[***]** (and will not be considered **[***]**, **[***]**, or **[***]**);

b. all Patent Rights Controlled by Biogen directed to or claiming the Biogen **[***]** as a composition of matter in a manner acceptable to a recognized patent office (*e.g.*, the United States Patent and Trademark Office, the European Patent Office, etc.), including by structure or sequence (the "***Biogen* [***] *Patents***"), will be solely owned by Biogen and will be considered Biogen **[***]** with respect to the **[***]** Collaboration Program (and will not be considered **[***]**). For clarity, Patent Rights that are not Biogen **[***]** Patent Rights will not be considered Biogen **[***]**, including Patent Rights solely directed to or solely claiming (i) **[***]** of Biogen **[***]** or (ii) **[***]** Biogen **[***]**, and such Patent Rights will continue to be Biogen **[***]**, **[***]** or **[***]**, as applicable; and

c. without limiting Paragraph 10(a) of this letter agreement, all Know-How that was discovered, developed, invented or created by or on behalf of either Party or its Affiliates under the Agreement or this letter agreement that **[***]** Biogen **[***]** will be considered **[***]** (as applicable).

11. **Biogen [***] Patent License**. Subject to the terms and conditions of the Agreement (including Ionis' exclusivity covenants under Section 2.1.1 (Exclusivity Covenants)), Biogen hereby grants Ionis an irrevocable, perpetual, worldwide non-exclusive, sublicensable (subject to the restrictions set forth in Section 4.3.4(c)), royalty-free license under any Biogen **[***]** Patent Controlled by Biogen or its Affiliates at any time during the Agreement Term to research, develop, manufacture, have manufactured and commercialize any:

a. products that include an Oligonucleotide as an active pharmaceutical ingredient (other than products that (i) include an Oligonucleotide that is designed to bind to the RNA that encodes the same target as a product that is being developed or commercialized by Biogen, its Affiliates or Sublicensee pursuant to an Option or exclusive license granted from Ionis under this Agreement or any Ionis/Biogen Additional Agreement or (ii) incorporate any Biogen **[***]**); and

b. Gene-Editing Products that do not incorporate any Biogen **[***]**.

12. **Third Party Obligations for [***]**. Notwithstanding Section 6.11 (Third Party Rights and Payment Obligations), so long as Biogen has an Option with respect to the **[***]** Strategy or a license under Section 4.1 (License Grants to Biogen) with respect to the **[***]** Collaboration Program, **[***]** will have the sole right and discretion, at its sole cost and expense, to acquire rights (whether by purchase, assignment, license, or otherwise) or other access to Patent Rights that are **[***]** the Biogen **[***]** that is incorporated into any Product under the **[***]** Collaboration Program and **[***]** will have no right of offset under Section 6.11 (Third Party Rights and Payment Obligations) for such Product Specific Payments, *provided*, *however*, the foregoing will not apply to any payments and other obligations to Third Parties to acquire rights (whether by purchase, assignment, license, or otherwise) or other access to Patent Rights that are **[***]** (a) **[***]** any Biogen **[***]**, or (b) **[***]** any Biogen **[***]** (and such Product-Specific Payments, in each case ((a) and (b)), will remain subject to the terms of Article 6 (Financial Provisions), to the extent applicable).

13. **Prosecution and Maintenance, Defense, and Enforcement of Patents**.

a. **Prosecution and Maintenance**.

i. *Prosecution and Maintenance of Biogen* **[***]** *Patents*. Notwithstanding any provision to the contrary set forth in Section 7.2 (Prosecution and Maintenance of Patents), Biogen will control and be responsible for all aspects of the Prosecution and Maintenance of all Biogen **[***]** Patents.

ii. *Prosecution and Maintenance of Biogen* **[***]** *Patents*. Prosecution and Maintenance of all Patent Rights that claim any Biogen **[***]** (the "***Biogen* [***] *Patents***") will be subject to the terms of Section 7.2 (Prosecution and Maintenance of Patents), to the extent applicable; *provided*, *however*, that notwithstanding any provision to the contrary set forth in Section 7.2.5 (Other Matters Pertaining to Prosecution and Maintenance of Patents) if (A) Ionis has the responsibility to Prosecute and Maintain any Biogen **[***]** Patents pursuant to Section 7.2 (Prosecution and Maintenance of Patents), (B) Biogen timely provides any comments with respect to any draft filing, communication, response, or strategy with respect to such Patent Rights in accordance with Section 7.2.5 (Other Matters Pertaining to Prosecution and Maintenance of Patents), and (C) Ionis decides not to incorporate any such comment timely provided by Biogen, then Biogen may refer the matter to Expert Resolution for resolution under Section 12.1.4 (Expert Resolution). If Biogen terminates the **[***]** Collaboration Program as described in Paragraph 14 or 15 of this letter agreement, then the terms of Section 7.2 (Prosecution and Maintenance of Patents) and this Paragraph 13(a)(ii) will survive such termination solely with respect to the Prosecution and Maintenance of the Biogen **[***]** Patents.

iii. *Coordination*. Notwithstanding Biogen's right to Prosecute and Maintain the Biogen **[***]** Patents or each Party's right to Prosecute and Maintain the Biogen **[***]** Patents to the extent provided in Section 7.2 (Prosecution and Maintenance of Patents) and this letter agreement, the Parties will, and will cause their Affiliates to, cooperate and implement reasonable patent filing and prosecution strategies (including filing divisionals, continuations or otherwise) to ensure that, to the extent reasonable and feasible, Patent Rights claiming the Biogen **[***]** and Patent Rights claiming any **[***]** directed to **[***]** under the **[***]** Collaboration Program are pursued in a manner that are not detrimental to each such set of Patent Rights.

b. **Enforcement**.

i. *Enforcement of Biogen* **[***]** *Patents*. Notwithstanding any provision to the contrary set forth in Section 7.5 (Enforcement of Patents against Competitive Infringement), for any Competitive Infringement with respect to a Product to the extent involving any Biogen **[***]** Patent, Biogen will have the sole right, but not the obligation, to institute, prosecute, and control any Proceeding with respect thereto by counsel of its own choice at its own expense.

ii. *Enforcement of Biogen* **[***]** *Patents*. Any Competitive Infringement with respect to a Product to the extent involving any Biogen **[***]** Patent will be subject to the terms of Section 7.5 (Enforcement of Patents against Competitive Infringement); *provided*, *however*, that notwithstanding any provision to the contrary set forth in Section 7.5 (Enforcement of Patents against Competitive Infringement), if (A) Ionis has the right to institute, prosecute, and control any Proceeding to the extent involving any such Biogen **[***]** Patent pursuant to Section 7.5 (Enforcement of Patents against Competitive Infringement), (B) Biogen timely provides any comments with respect to filings, submissions and communications related to such Proceeding in accordance with Section 7.5 (Enforcement of Patents against Competitive Infringement), and (C) Ionis decides not to incorporate any such comment timely provided by Biogen, then Biogen may refer the matter to Expert Resolution for resolution under Section 12.1.4 (Expert Resolution).

14. **Consequences of Termination or Failure to Designate a Development Candidate Prior to License Effective Date**. If (A) the Agreement with respect to the **[***]** Collaboration Program or the **[***]** Collaboration Program is terminated by Biogen pursuant to Section 10.3.2 (Biogen's Termination for Convenience) before the License Effective Date for such Collaboration Program or the Option with respect to such Collaboration Program expires unexercised, (B) Biogen has not reasonably determined (and Biogen has not so notified Ionis in writing of such determination and the rationale therefor, which such notice must be delivered (I) in the event Biogen so terminates such Collaboration Program, then together with such notice of termination, or (II) in the event the Option with respect to such Collaboration Program expires unexercised, then prior to the expiration of the Option (each of (I) and (II), the "**Reversion Notification Deadline**")) that any further Research, Development, Manufacture, and Commercialization of Terminated Strategy Products that are the subject of such Collaboration Program **[***]** (subject to Paragraph 16 of this letter agreement), and (C) such termination of the Agreement is not due to **[***]** that are reasonably demonstrated by Biogen to Ionis on or prior to the applicable Reversion Notification Deadline, then, in addition to the terms set forth in Section 10.6.1 (In General), the following terms will apply:

a. Biogen's Option under Section 3.1 (Option) will expire with respect to such Collaboration Program;

b. Notwithstanding anything to the contrary set forth in Section 2.1.1 (Exclusivity Covenants) and regardless of whether Biogen has exercised an Option for another Collaboration Program directed to **[***]**, Ionis will be free to Develop, Manufacture and Commercialize Terminated Strategy Product(s) with respect to such Collaboration Program, on its own or with a Third Party, *provided*, *however*, that Ionis will not, on its own or with any Third Party, change, use an alternate, or in any way modify, any Terminated Strategy Product, including any Biogen **[***]** included therein, that is incorporated into any Terminated Strategy Product, except for any Permitted Changes in Form. For clarity, the terms of Section 2.1.1 (Exclusivity Covenants) will continue to govern the Development and Commercialization by Ionis or its Affiliates of any Products directed to **[***]** that are not Terminated Strategy Products, to the extent applicable.

c. To the extent requested by Ionis, Biogen will promptly transfer to Ionis all data, results, and information (including Biogen's Confidential Information and any regulatory documentation (including drafts)) related to the testing and Clinical Studies for such Terminated Strategy Products in the possession of Biogen or its contractors, to the extent such data, results, and information were generated by or on behalf of Biogen under the Agreement; and Ionis will pay all out-of-pocket direct Third Party costs and expenses in transferring such data, results and information together with the Biogen FTE Cost in transferring such data, results and information.

d. The provisions of Section 10.6.3(h) will apply solely with respect to such Terminated Strategy Products (and for clarity, not with respect to other Discontinued Products that are the subject of such Collaboration Program), *mutatis mutandis*, and solely for the purposes of Section 10.6.3(h), **[***]** will be considered a Terminated Target thereunder, *provided*, *however*, that the terms of Section 10.6.3(h)(v) will not apply to, and Biogen will not be required to provide to Ionis, any Regulatory Materials that solely relate to the Biogen **[***]** incorporated into the Terminated Strategy Product, unless requested by a Regulatory Authority, in which case Biogen will provide such information to Ionis, solely for the purposes of submitting such information to such Regulatory Authority, subject to Article 11 (Confidentiality).

e. For the purposes of this letter agreement, "***Terminated Strategy Products***" means, with respect to the **[***]** Collaboration Program or the **[***]** Collaboration Program (as applicable), all Products that (i) are the subject of such Collaboration Program and that are in existence as of the effective date of termination of the Agreement with respect to such Collaboration Program, (ii) only utilize the Strategy of such Collaboration Program (*i.e.*, as such Strategy is defined in the recitals to this letter agreement), and (iii) are either in the form that such Products exist as of such effective date of termination or are any Permitted Changes in Form.

15. **Consequences of Termination After License Effective Date**. If (A) the Agreement with respect to the **[***]** Collaboration Program or the **[***]** Collaboration Program is terminated by Biogen under Section 10.3.2 (Biogen's Termination for Convenience) after the License Effective Date for such Collaboration Program, (B) Biogen has not reasonably determined (and Biogen has not so notified Ionis in writing of such determination and the rationale therefor, which such notice must be delivered on or prior to the applicable Reversion Notification Deadline) that any further Research, Development, Manufacture, and Commercialization of Terminated Strategy Products that are the subject of such Collaboration Program **[***]** (subject to Paragraph 16 of this letter agreement), and (C) such termination of the Agreement is not due to **[***]** that are reasonably demonstrated by Biogen to Ionis on or prior to the applicable Reversion Notification Deadline, then, in addition to the terms set forth in Section 10.6.1 (In General), the following terms will apply:

a. The applicable licenses granted by Ionis to Biogen under the Agreement will terminate with respect to such Collaboration Program. Biogen, its Affiliates and Sublicensees will cease selling the Products that are the subject of such Collaboration Program, unless Ionis elects to have Biogen continue to sell such Products as part of the Transition Services to the extent provided in Section 10.6.6 (Transition Services).

b. Notwithstanding anything to the contrary set forth in Section 2.1.1 (Exclusivity Covenants) and regardless of whether Biogen has exercised an Option for another Collaboration Program directed to **[***]**, Ionis will be free to Develop, Manufacture and Commercialize Terminated Strategy Product(s) with respect to such Collaboration Program, on its own or with a Third Party, *provided*, *however*, that Ionis will not, on its own or with any Third Party, change, use an alternate, or in any way modify, any Terminated Strategy Product, including any Biogen **[***]** included therein, that is incorporated into any Terminated Strategy Product, except for any Permitted Changes in Form. For clarity, the terms of Section 2.1.1 (Exclusivity Covenants) will continue to govern the Development and Commercialization by Ionis or its Affiliates of any Products directed to **[***]** that are not Terminated Strategy Products, to the extent applicable.

c. The provisions of Section 10.6.4(d), Section 10.6.4(e) and Section 10.6.4(f) will apply solely with respect to such Terminated Strategy Products (and for clarity, not with respect to other Discontinued Products that are the subject of such Collaboration Program), *mutatis mutandis*, and solely for the purposes of Section 10.6.4(d), Section 10.6.4(e) and Section 10.6.4(f), **[***]** will be considered a Terminated Target thereunder, *provided*, *however*, that (i) for the purposes of Section 10.6.4(f), to the extent requested by Ionis, Biogen will only be required to assign to Ionis any manufacturing agreements to the extent solely related to the Terminated Strategy Products (and, for clarity, will not be obligated to assign to Ionis any manufacturing agreements that relate to **[***]** generally), (ii) following the assignment back by Biogen to Ionis of the Product-Specific Patents described in Section 10.6.4(d)(v), Ionis will and hereby does grant to Biogen a worldwide, non-exclusive, sublicensable license under such Patent Rights to research, Develop, Manufacture, have Manufactured, register, market, and Commercialize any Biogen **[***]**, whether alone or in combination with any other compound or conjugate, but excluding Terminated Strategy Products, and (iii) the terms of Section 10.6.4(d)(ix) will not apply to the Prosecution and Maintenance of any Biogen **[***]** Patents (and for clarity, the terms of Paragraph 13(a)(ii) of this letter agreement will apply to the Prosecution and Maintenance of such Patent Rights).

16. **Disputes Regarding Biogen Notification of [***] Terminated Strategy Products**. If Ionis disputes Biogen's determination under clause (B) of Paragraph 14 or clause (B) of Paragraph 15 of this letter agreement that any further Research, Development, Manufacture, and Commercialization of Terminated Strategy Products that are the subject of a terminated **[***]** Collaboration Program **[***]**, then Ionis may refer the matter to Expert Resolution for resolution under Section 12.1.4 (Expert Resolution).

17. **Publications Prior to License Effective Date**. Notwithstanding any provision to the contrary set forth in Section 11.4 (Press Release; Publications; Disclosure of Agreement):

    a. Solely with respect to the **[***]** Collaboration Program, the terms of Section 11.4.4 (Prior to License Effective Date) are hereby amended and replaced with the following: "prior to the License Effective Date for the **[***]** Collaboration Program, neither Party will have sole right to issue press releases, publish, present or otherwise disclose the progress and results regarding such Products to the public without the prior written consent of the other Party"; and

    b. Biogen will have the sole right to issue press releases, publish, present, or otherwise disclose the progress and results regarding the Biogen **[***]** if such press release, publication, presentation, or other disclosure does not disclose any progress or results regarding any **[***]** that is incorporated into any Product under the **[***]** Collaboration Program.

The terms of Section 12.14 (Interpretation) will govern the terms of this letter agreement. Except as otherwise expressly set forth herein, the provisions of the Agreement will remain in full force and effect and each Party reserves its rights thereunder. In the event of any express conflict or inconsistency between this letter agreement and the Agreement, the terms of this letter agreement will apply.

If you accept the terms and conditions set forth in this letter agreement, please so indicate by executing a copy of this letter agreement and returning it to Ionis. This letter agreement may be executed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation which may result from electronic transmission, store and printing of copies of this letter agreement from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

[*SIGNATURE PAGE FOLLOWS*]

Sincerely,

/s/Brett Monia
Brett Monia
Chief Executive Officer
Ionis Pharmaceuticals, Inc.

AGREED AND CONFIRMED ON BEHALF OF BIOGEN MA INC.:

By: /s/Anabella Villalobos
Name: Anabella Villalobos
Title: Senior Vice President, Biotherapeutics & Medicinal Sciences
Date: December 31, 2020

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

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 and 333-188407) and in the related Prospectuses, as applicable, and in the Registration Statements on Form S-8 (Nos.333-05825, 333-55683, 333-40336, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777, 333-151996, 333-160269, 333-168674, 333-176136, 333-184788, 333-190408 and 333-207900) of Ionis Pharmaceuticals, Inc. of our reports dated February 24, 2021, 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, 2020.

/s/ ERNST & YOUNG LLP

San Diego, California
February 24, 2021

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: February 24, 2021

/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: February 24, 2021

/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, 2020, 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: February 24, 2021

/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.