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, 2017

☐ **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 0-19125

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	Name of each exchange on which registered
Common Stock, $.001 Par Value	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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post such files). Yes ☐ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ☐	Accelerated filer ☐
Non-accelerated filer ☐ (Do not check if a smaller reporting company)	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 7(a)(2)(B) of the Securities Act. ☐

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

The approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on The Nasdaq Global Select Market was $5,158,628,572 as of June 30, 2017.*

The number of shares of voting common stock outstanding as of February 20, 2018 was 125,403,219.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 9, 2018 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on May 23, 2018 are incorporated by reference into Part III of this Report.

* Excludes 22,738,285 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, 2017. 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, inotersen, volanesorsen and our technologies and products in development, including the business of Akcea Therapeutics, Inc., our majority owned affiliate. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report on Form 10-K, including those identified in Item 1A entitled "Risk Factors". Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

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

TRADEMARKS

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

CORPORATE INFORMATION

We incorporated in California in 1989 and in January 1991 we changed our state of incorporation to Delaware. In December 2015, we changed our name to Ionis Pharmaceuticals, Inc. from Isis Pharmaceuticals, Inc. Our principal offices are in Carlsbad, California. We make available, free of charge, on our website, *www.ionispharma.com*, our reports on Forms 10-K, 10-Q, 8-K and amendments thereto, as soon as reasonably practical after we file such materials with the Securities and Exchange Commission. Any information that we include on or link to our website is not a part of this report or any registration statement that incorporates this report by reference. You may also read and copy our filings at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-732-0330. The SEC also maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that site is *www.sec.gov*.

In December 2014, we formed Akcea Therapeutics, Inc., as a Delaware corporation, with its principal office in Cambridge, Massachusetts. Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea's stock. After Akcea's IPO, we owned approximately 68 percent of Akcea.

IONIS PHARMACEUTICALS, INC.
FORM 10-K
For the Fiscal Year Ended December 31, 2017
Table of Contents

PART I

Item 1. Business

Overview

We are leaders in discovering and developing RNA-targeted therapeutics. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics. Using this platform, we have developed a large, diverse and advanced pipeline of potentially first-in-class and/or best-in-class drugs that we believe can provide high value for patients with significant unmet medical needs. In this way, we believe we are fundamentally changing medicine with the goal to transform the lives of those suffering from severe, often life-threatening, diseases.

We made significant progress toward this goal with the commercial launch of SPINRAZA (nusinersen) for the treatment of spinal muscular atrophy, or SMA, in pediatric and adult patients. SMA is a leading genetic cause of death in infants marked by progressive, debilitating muscle weakness. SPINRAZA became the first and only approved drug to treat people with SMA and is now the standard of care for this debilitating disease. Our partner, Biogen, is responsible for global commercial activities. In January 2018, Biogen reported that SPINRAZA was available in over 30 global markets. Additionally, Biogen is continuing to purse regulatory approvals for SPINRAZA in countries around the world. In 2017, we earned $113 million in commercial revenue from SPINRAZA royalties. We also earned a $50 million milestone payment for the EU approval of SPINRAZA and a $40 million milestone payment for SPINRAZA pricing approval in Japan.

Our pipeline also contains two near-term, potentially transformative medicines for two different severe and rare diseases, each with significant commercial potential, inotersen and volanesorsen. We believe inotersen has the potential to become the preferred treatment option for many people with hereditary TTR amyloidosis, or hATTR. Our goal is to free these people from the burden of their disease. hATTR is a debilitating, progressive, fatal disease in which patients experience a progressive buildup of amyloid plaque deposits in tissues throughout the body. In May 2017, we reported positive top-line data from our Phase 3 study of inotersen, NEURO-TTR, in patients with hATTR with polyneuropathy. More than half of these patients also have cardiomyopathy. We are advancing inotersen to the market based on the positive data from our NEURO-TTR study. In November 2017, we filed for marketing authorization for inotersen to treat people with hATTR in the U.S. and EU. The Food and Drug Administration, or FDA, accepted the inotersen New Drug Application, or NDA, for Priority Review and set a Prescription Drug User Fee Act, or PDUFA, date of July 6, 2018. The European Medicines Agency, or EMA, also granted accelerated assessment to inotersen, which may reduce standard review time. We are on track in our pre-commercial preparations for a potential launch in mid-2018, if inotersen is approved. Our goals for inotersen are to maximize the commercial potential of the drug, maximize our commercial participation and continue to build our TTR franchise by moving IONIS-TTR-L_{Rx} forward rapidly. We plan to commercialize inotersen in North America ourselves and to seek a commercial partner in other geographic regions.

Akcea Therapeutics, Inc., or Akcea, our affiliate focused on developing and commercializing drugs for serious cardiometabolic diseases caused by lipid disorders, is working closely with us to develop volanesorsen to treat two severe and rare, genetically defined diseases, familial chylomicronemia syndrome, or FCS, and familial partial lipodystrophy, or FPL. FCS and FPL are orphan diseases characterized by severely high triglyceride levels that result in severe, daily symptoms and a high risk of life-threatening pancreatitis. We estimate that FCS and FPL each affect 3,000 to 5,000 people globally. The clinical development program for volanesorsen consists of three Phase 3 studies called APPROACH, BROADEN and COMPASS. In the first quarter of 2017, we and Akcea reported positive Phase 3 data from the APPROACH study in patients with FCS. In December 2016, we and Akcea reported positive results from the Phase 3 COMPASS study in patients with triglycerides above 500 mg/dL. Based on the positive data from our Phase 3 studies, Akcea filed for marketing authorization for volanesorsen in the U.S., EU and Canada in the third quarter of 2017. The FDA set a PDUFA date of August 30, 2018 for volanesorsen and an advisory committee meeting is scheduled for May 10, 2018. Volanesorsen was granted Priority Review in Canada. Akcea is on track in its pre-commercial preparations for a potential launch in mid-2018, if volanesorsen is approved.

In addition to preparing to commercialize volanesorsen, Akcea is focused on developing and commercializing three other clinical-stage drugs for serious cardiometabolic diseases caused by lipid disorders: AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}, each of which could potentially treat multiple patient populations. Moving these drugs into Akcea allows us to retain substantial value from them and ensures our core focus remains on innovation. Akcea completed its initial public offering, or IPO, and a concurrent private placement with Novartis in July 2017, raising over $180 million in net proceeds. As a result of Akcea's IPO and as of February 2018, we owned approximately 68 percent of Akcea.

We are addressing a broad spectrum of diseases that affect millions of people, such as cardiovascular disease, clotting disorders, Alzheimer's and Parkinson's disease. We also are addressing rare diseases, such as acromegaly, amyotrophic lateral sclerosis, beta-thalassemia and Huntington's disease. We are continuing to advance our mid-stage drugs in development, which have the potential to enter late-stage clinical development and progress toward the market over the next several years, like IONIS-HTT_{Rx}. IONIS-HTT_{Rx} is the first drug in clinical development to target the cause of Huntington's disease, or HD, by reducing the production of toxic mutant huntingtin, or mHTT, protein. In December 2017, following successful completion of the Phase 1/2 study in which IONIS-HTT_{Rx} demonstrated dose-dependent reductions of the mHTT protein in patients with HD, Roche licensed IONIS-HTT_{Rx} for $45 million. We plan to report data from this Phase 1/2 study in early 2018. We have also initiated an open-label extension, or OLE, study for people who participated in the Phase 1/2 study. Roche is now responsible for all IONIS-HTT_{Rx} development, regulatory and commercialization activities and costs.

The depth of our knowledge and expertise with antisense technology, together with our strong financial position, provides us with the flexibility to determine the optimal development and commercialization strategy to maximize the near and longer-term value of our drugs. We have distinct partnering strategies that we employ based on the specific drug, therapeutic area and expertise and resources our potential partners may bring to the collaboration. For some drugs, we may choose to develop and commercialize them through wholly owned subsidiaries or majority owned affiliates like Akcea. In general, these are drugs, like volanesorsen, that we have the internal expertise to advance, that have a clear development path with manageable costs and that have the potential for initial rare disease indications. For other drugs, we may form partnerships that enable us to leverage our partner's global expertise and resources needed to support large commercial opportunities, as we did with Bayer and Novartis.

We have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our drugs, advancing our technology and preparing to commercialize our products. Our partners bring substantial resources and expertise that augment and build upon our internal capabilities. We have strategic partnerships with Biogen and AstraZeneca through which we can broadly expand our drug discovery efforts to new disease targets in specific therapeutic areas. We also have partnerships with Bayer, GSK, Janssen, Novartis and Roche. Each of these companies brings significant expertise and global resources to develop and potentially commercialize the drugs under these partnerships. In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. As a leader in the cardiovascular disease space, Novartis brings significant resources and expertise that should support the development and commercialization of these two drugs for significant high-risk patient populations. The collaboration with Novartis should enable us to accelerate the development of these drugs for broader patient populations as Novartis plans to conduct a cardiovascular outcomes study for each of these drugs following successful completion of Phase 2 dose-ranging studies. In addition, Akcea has the right to co-commercialize these drugs using its specialized sales force focused on lipid specialists in select markets. We also form early stage research and development partnerships that allow us to expand the application of our technology to new therapeutic areas. For example, under our collaboration with Janssen, we have licensed IONIS-JBI1-2.5$_{Rx}$ and IONIS-JBI2-2.5$_{Rx}$, two antisense drugs we discovered to treat autoimmune disorders in the gastrointestinal, or GI, tract. Our collaboration with Janssen combines our RNA-targeted technology platform and Janssen's expertise in autoimmune disorders and therapeutic formulation. Lastly, we also work with a group of companies that can develop our drugs and utilize our technologies outside our primary areas of focus. We refer to these companies as satellite companies.

Through our partnerships, we have created a broad and sustaining base of research and development, or R&D, revenue in the form of license fees, upfront payments and milestone payments while spending prudently to advance our pipeline and technology. Our R&D revenue has consistently grown year over year since 2011. In 2017, we earned $386 million in R&D revenue. Moreover, we have the potential to earn over $13 billion in future milestone payments and licensing fees from our current partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through royalty arrangements. In late 2016, we began adding commercial revenue from SPINRAZA royalties to our existing R&D revenue base. Looking forward, we have the potential to increase our commercial revenue from SPINRAZA royalties from the continued growth we expect in the U.S., EU and in other markets globally. We also have the potential to further increase our commercial revenue with volanesorsen and inotersen. We believe we have the key elements in place to achieve sustained, long-term financial growth, with multiple drivers of revenue; a mature, broad and rapidly-advancing clinical pipeline; a partnership strategy that leverages our partner resources; and an innovative drug discovery technology platform that we continue to deploy across a range of therapeutic areas to address both rare and large patient populations.

Recent Pipeline and Technology Highlights

- *SPINRAZA for SMA – one of the most successful orphan drug launches in history*
  - SPINRAZA, commercialized by Biogen, generated 2017 global sales of $884 million
  - Results from the ENDEAR study and CHERISH study, in which people with infantile-onset and later-onset SMA, respectively, were treated with SPINRAZA, were published in *The New England Journal of Medicine*
  - Prestigious 2017 Prix Galien USA Award for Best Biotechnology Product awarded to us and Biogen for SPINRAZA
  - New collaboration with Biogen initiated to discover new antisense drugs with enhanced properties to treat SMA

- *Inotersen for hATTR – potential to transform the lives of people with hATTR*
  - Marketing applications accepted, no FDA Advisory Committee recommended, Priority Review in the U.S. and Accelerated Assessment in the EU
  - Preparations for global launch, planned for mid-2018, progressing
  - Phase 3 NEURO-TTR study met both primary endpoints demonstrating benefit compared to placebo in multiple measures of quality of life and disease severity; 50 percent of inotersen-treated patients experienced improvement from baseline in quality of life

- *Volanesorsen for FCS and FPL – potential first treatment for people with FCS*
  - Marketing applications accepted in the U.S., EU and Canada with Promising Innovative Medicine designation in the UK and Priority Review in Canada
  - Preparations for global launch for FCS, planned for mid-2018, progressing
  - Phase 3 APPROACH study met primary endpoint of reducing triglyceride levels in people with FCS

- *Pipeline Programs (early and mid-stage) – advancing wholly owned and partnered programs*
    - Positive results from seven Phase 2 studies reported, including:
        - Positive data from Phase 1/2 study of IONIS-STAT3-2.5$_{Rx}$ in combination with AstraZeneca's Imfinzi reported for people with head and neck cancer
        - Robust, dose-dependent reductions of mHTT observed in people with Huntington's disease treated with IONIS-HTT$_{Rx}$
    - Positive clinical data on five LICA drugs reported, demonstrating consistent, positive performance and sustained target reduction with potential for monthly or less frequent dosing
    - Positive results from six Phase 1 studies reported
    - Nine Phase 2 studies and four Phase 1 studies initiated across multiple therapeutic areas to treat people with both broad and rare diseases

Drug Discovery and Development

Introduction to Drug Discovery

Proteins are essential working molecules in a cell. Almost all human diseases result from inappropriate protein production, improper protein activity or loss of a protein. Scientists use traditional drug discovery methods to design drugs to interact with the proteins in the body that are supporting or causing a disease. Antisense drugs are different from traditional small molecule or antibody drugs because antisense drugs can modify the production of proteins by targeting RNAs. In this way, antisense drugs can reduce the production of a disease-causing protein, modify the protein produced or increase the production of a protein that, when absent, causes disease. Antisense drugs also can treat disease by targeting and reducing RNAs that may be causing disease (so called "toxic RNAs"). RNAs are naturally occurring molecules in the body that primarily act as messengers that carry the information the cell needs to produce proteins from the DNA/genes to the protein making complex in the cell. When our antisense drugs 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 RNA.

Our Development Projects

We are the leader in the discovery and development of an exciting class of RNA-targeted drugs called antisense oligonucleotide, or ASO, drugs, or just antisense drugs. With our proprietary drug discovery platform, we can rapidly identify drugs from a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas in which our drugs will work best, efficiently screening many targets in parallel and carefully selecting the best drug candidates. By combining this efficiency with our rational approach to selecting disease targets, we have built a large and diverse portfolio of drugs we designed to treat a variety of health conditions, with an emphasis on severe and rare diseases, including neurodegenerative diseases, cardiometabolic diseases, and cancer. We are developing antisense drugs for systemic and local delivery (e.g., intrathecal for CNS diseases, intraocular for ophthalmic diseases, oral local for gastrointestinal diseases and aerosol for diseases of the lung). We expect to continue to add new drugs to our pipeline, building a broad proprietary portfolio of drugs to treat many diseases and creating opportunities to generate substantial revenue. We also continue to improve our scientific understanding of our drugs, including how our drugs impact the biological processes of the diseases we target.

With our expertise in discovering and characterizing novel antisense drugs, our scientists can optimize the properties of our antisense drugs for use with particular targets. Our scientists have made significant advances in chemical modifications we use in our antisense drugs, such as with our Generation 2+ antisense drugs, which have increased potency and an improved side effect profile over our earlier generation drugs. 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 drugs, which broadens the tissues in which our drugs can work. We currently have nine Generation 2.5 drugs in development, and we expect that more of our future drugs will incorporate our Generation 2.5 chemistry. In addition to improving the chemical foundation of our drugs, we have also created LIgand-Conjugated Antisense, or LICA, technology, which we design to enhance the effective uptake of our drugs in particular tissues.

With our LICA technology we attached specific chemical structures or molecules to our antisense drugs. With our first LICA conjugate, a complex sugar-like molecule called N-acetylgalactosamine, or GalNac, we have shown an increase in drug potency from 20 to over 30-fold for liver targets, compared to non-conjugated antisense drugs. We currently have 12 LICA drugs in development, including IONIS-AZ4-2.5-L$_{Rx}$, a drug that combines our Generation 2.5 and LICA technology.

We have utilized our chemistry advancements, such as Generation 2.5 and LICA, to expand the therapeutic and commercial opportunities of our pipeline. These advancements, along with the manufacturing and analytical processes that are the same for all of our drugs, 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 drugs.

The above table lists the drugs in our pipeline that are in clinical trials, in registration for marketing authorization, or commercialized. The table includes the disease indication, a partner (if the drug is partnered), and the development status of each drug. Typically, the names of our drugs incorporate the target of the drug. For example, with IONIS-HTT$_{Rx}$, the RNA produced from the huntingtin gene, represented by the acronym HTT, is the target of the drug. Unless indicated otherwise, the majority of the drugs in our pipeline are Generation 2+ antisense drugs. We differentiate drugs that Akcea is developing by using "AKCEA", instead of "IONIS" at the beginning of the drug name, such as AKCEA-ANGPTL3-L$_{Rx}$. We differentiate our Generation 2.5 drugs by adding a "2.5" notation at the end of the drug name, such as IONIS-STAT3-2.5$_{Rx}$. We differentiate our LICA drugs by adding an "L" at the end of the drug name, such as IONIS-PKK-L$_{Rx}$. In 2016, we added IONIS-AZ4-2.5-L$_{Rx}$, a drug that combines our Generation 2.5 chemistry and LICA technology, to our preclinical pipeline. As the drugs in our pipeline advance in clinical development, we will adopt nonproprietary names given to each drug from the United States Adopted Names Council. For example, volanesorsen is a nonproprietary name that we obtained for IONIS-APOCIII$_{Rx}$. Once we or our partners establish a brand name, we will adopt the brand name. For example, SPINRAZA is the brand name for nusinersen.

With a pipeline as large and advanced as ours, we have a number of clinical events each year as we initiate new clinical studies, complete and report data from clinical studies, and add numerous new drugs to our pipeline. In 2018, we plan to initiate five Phase 2 studies, report data on six Phase 2 studies and multiple proof-of-concept initial clinical trials and add three to five new drugs into development.

Our Marketed Drug

SPINRAZA – SPINRAZA (nusinersen) injection, for intrathecal use is a survival motor neuron-2 (SMN2)-directed antisense oligonucleotide indicated for the treatment of SMA in pediatric and adult patients. In July 2016, Biogen licensed SPINRAZA from us. We have transitioned all SPINRAZA development activities to Biogen as they are now responsible for all global development, regulatory and commercialization activities and costs. In January 2018, Biogen reported that SPINRAZA was available in over 30 global markets.

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, individuals with the most severe type of SMA, infantile-onset 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 survival motor neuron, or 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 infantile-onset, or Type 1, SMA, the most severe life-threatening form of the disease, 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, produce greater amounts of SMN protein and have less severe, but still life-altering, forms of SMA.

SPINRAZA is administered via intrathecal injection, which delivers therapies directly to the cerebrospinal fluid, or CSF, around the spinal cord, where motor neurons degenerate in people with SMA due to insufficient levels of SMN protein.

The safety and efficacy of SPINRAZA has been evaluated from multiple clinical studies in more than 270 patients, including two Phase 3 studies: ENDEAR, a randomized controlled study evaluating SPINRAZA in patients with infantile-onset SMA, and CHERISH, a randomized controlled study evaluating SPINRAZA in patients with later-onset SMA; as well as open-label studies in pre-symptomatic and symptomatic patients with, or likely to develop, Types 1, 2 and 3 SMA.

In the ENDEAR end of study analysis, or EOS, a statistically significant greater percentage of children with infant-onset SMA achieved improvement in motor milestones compared to untreated patients, with some infants in the SPINRAZA group achieving full head control, the ability to roll, sitting, and standing. Additionally, infants treated with SPINRAZA demonstrated a statistically significant improvement in event-free survival compared to untreated patients. In November 2017, results from EOS analysis, from the ENDEAR study, including the pre-specified primary endpoint, time to death or permanent ventilation, were published in *The New England Journal of Medicine*. SPINRAZA met the pre-specified primary endpoint at the ENDEAR EOS, demonstrating a statistically significant 47 percent reduction in the risk of death or permanent ventilation ($p<0.01$). In October 2017, Biogen presented a new analysis from the Phase 3 ENDEAR study that showed infants with SMA who initiated treatment earlier in the disease demonstrated greater benefit and improvement in motor function outcomes.

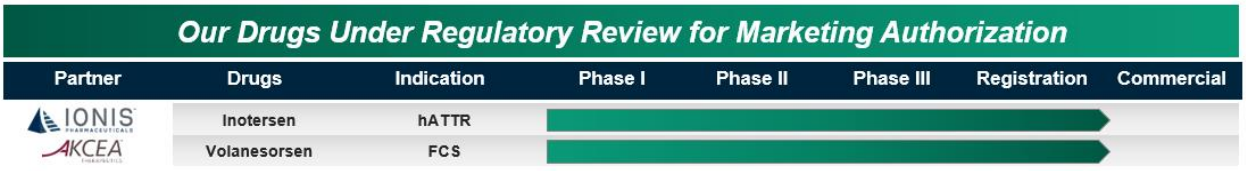
In the CHERISH pre-specified interim analysis, there was a statistically significant and clinically meaningful improvement in motor function in children with later-onset SMA treated with SPINRAZA compared to untreated children. In an EOS analysis, children receiving SPINRAZA experienced a highly statistically significant improvement in motor function compared to those who did not receive treatment. *The New England Journal of Medicine* published these results in February 2018.

Additionally, Biogen conducted NURTURE, a Phase 2 open-label study in pre-symptomatic infants. In an interim analysis, SPINRAZA-treated pre-symptomatic infants with SMA 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. Three infants experienced AEs considered possibly related to SPINRAZA, all of which were resolved.

Further, in open-label studies, some patients achieved milestones that they would not be expected to achieve, such as the ability to sit unassisted, stand or walk, and maintained milestones at ages that they would expect to lose. The overall findings in the combined clinical studies to date support the effectiveness of SPINRAZA across the range of patients with SMA, and appear to support the early initiation of treatment.

In all clinical studies, SPINRAZA demonstrated a favorable safety profile. The most common side effects of SPINRAZA included lower and upper respiratory infections, constipation, headache, back pain, and post-lumbar puncture syndrome. For additional safety information, please see www.spinraza.com.

Our Drugs Under Regulatory Review for Marketing Authorization



We have two drugs for which we successfully completed pivotal Phase 3 studies and are now under regulatory review for marketing authorization: inotersen and volanesorsen. These drugs are potentially transformative medicines for two different severe and rare diseases, each with significant commercial potential.

Inotersen – Inotersen is a Generation 2+ antisense drug we designed to treat people with hereditary TTR amyloidosis, or hATTR, a rare, progressive, fatal disease.

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

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 symptom or the other is diagnosed first and is more pronounced. Polyneuropathy due to hATTR is caused by the accumulation of misfolded mutated TTR protein in the peripheral nerves. People with polyneuropathy due to hATTR experience ongoing debilitating nerve damage throughout their body resulting in the progressive loss of sensation in the extremities that progresses centrally, and progressive loss of motor functions, such as walking. These people also accumulate TTR in other major organs, which progressively compromise their function and eventually leads to death within five to fifteen years of disease onset. ATTR cardiomyopathy is caused by the accumulation of misfolded TTR protein in the cardiac muscle. ATTR can also result from normal, non-mutant, TTR protein forming fibrils, primarily in the heart. This form of the disease is referred to as wt-ATTR. It is estimated that more than 200,000 people worldwide have wt-ATTR. People with hATTR cardiomyopathy and wt-ATTR experience ongoing debilitating heart damage resulting in progressive heart failure, which results in death within 3 to 5 years from disease onset.

In May 2017, we completed the NEURO-TTR study, a randomized, double-blinded, placebo-controlled, international Phase 3 study in patients with polyneuropathy due to hATTR. Results from the study demonstrated benefit compared to placebo across both primary endpoints of the study: the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy, or Norfolk QoL-DN, and the modified Neuropathy Impairment Score +7, or mNIS+7, at both eight and 15 months of treatment. In addition, consistent and significant benefit was observed in both the Norfolk-QoL-DN and mNIS+7, independent of disease stage, types of mutation, previous treatment with TTR protein stabilizers or presence of cardiomyopathy. Inotersen-treated patients benefited significantly in the quality of life primary endpoint with 50 percent demonstrating improvement from baseline. Inotersen-treated patients achieved a mean 11.68 point benefit in the Norfolk QoL-DN score at 15 months of treatment compared to placebo-treated patients (mean change from baseline of 0.99 vs. 12.67, p=0.0006). In addition, clinically meaningful benefit compared to placebo was observed in the SF-36 physical component score, a measure of general health and quality of life. Inotersen-treated patients also benefited significantly in the co-primary endpoint of disease control, mNIS+7, with a mean 19.73-point benefit observed after 15 months of treatment, compared to placebo-treated patients (p = 0.00000004).

Two key safety issues were identified during the study: thrombocytopenia and safety signals related to renal function. Enhanced monitoring was implemented during the study to support early detection and management of these issues. Serious platelet and renal events were infrequent and manageable with routine monitoring, which has proven effective since implementation. Other serious adverse events were observed in 24.1 percent of inotersen-treated patients and 21.7 percent of placebo-treated patients. No cumulative toxicities have been identified with long-term exposure.

Adverse events occurring in ≥ 10 percent of patients and twice as frequently in inotersen-treated patients compared with placebo-treated patients, included thrombocytopenia/platelet count decreases, nausea, pyrexia, chills, vomiting, and anemia. Injection site reactions accounted for less than 1 percent of all injections and were mild or moderate in severity. There were no discontinuations due to injection site reactions.

The overall mortality rate in the NEURO-TTR study was 2.9 percent and was lower than mortality rates reported in other studies in patients with hATTR. There was a total of five deaths in the study, five (4.7 percent) in the inotersen arm and zero in the placebo arm. Four deaths in the inotersen arm were associated with disease progression and considered unrelated to treatment. As previously reported, there was one fatal intracranial hemorrhage in conjunction with serious thrombocytopenia. No serious thrombocytopenia was observed following implementation of more frequent monitoring.

Inotersen is currently under regulatory review for marketing authorization in the U.S. and EU for the treatment of hATTR. Inotersen has been granted Priority Review by the FDA and has a PDUFA date of July 6, 2018. The EMA also granted accelerated assessment to inotersen, which may reduce standard review time. In addition, an open-label extension study, or OLE, is ongoing for patients who have completed the NEURO-TTR study, in which all patients are treated with inotersen. We have also opened an expanded access program, or EAP, for eligible patients, beginning with sites in the U.S.

We plan to commercialize inotersen in North America ourselves and to seek a commercial partner in other geographic regions.

Volanesorsen – Volanesorsen is a Generation 2+ antisense drug Akcea and we are developing to treat people with FCS and FPL, which are severe, rare, genetically defined diseases characterized by extremely elevated triglyceride levels and a high risk of life-threatening pancreatitis.

Due to the high levels of triglycerides in their blood, people with FCS may suffer from 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 have to adhere to a very strict, low-fat diet. As a result of these factors, people with FCS and FPL are often unable to work, adding to the burden of the disease. While all the complications of FCS or FPL cause patients to have a lower quality of life, pancreatitis is the most serious consequence of the disease. In severe cases, patients can have bleeding into the pancreas, serious tissue damage, infection and cyst formation, as well as damage to other vital organs such as the heart, lungs and kidneys. We estimate there are 3,000 to 5,000 people with FCS in treatable markets and an additional 3,000 to 5,000 people with FPL globally.

Volanesorsen acts to reduce triglyceride levels by inhibiting the production of apolipoprotein C-III, or apoC-III, a protein that is a key regulator of triglyceride clearance. 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, volanesorsen is able to increase triglyceride clearance in people with FCS, reducing their triglyceride levels.

The marketing application for volanesorsen for the treatment of FCS is based on data from the Phase 3 APPROACH and COMPASS studies. The pivotal APPROACH study, 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), 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 volanesorsen-treated patients. Akcea observed 50 percent of treated patients achieved triglyceride levels below 500 mg/dL, a commonly accepted threshold for pancreatitis risk. In addition, in the APPROACH study, treatment with volanesorsen 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. The COMPASS study, a six-month randomized placebo-controlled study in 113 patients with very high triglycerides (>500 mg/dL), also achieved its primary endpoint of reduction in triglycerides at three months, with a 71 percent mean reduction in triglycerides. In the COMPASS study, treatment with volanesorsen was associated with a statistically significant reduction in on-study pancreatitis attacks.

The most common adverse event in the studies was injection site reactions, which were mostly mild. In addition, declines in platelet counts were observed in many patients and some patients discontinued the study because of platelet declines. These platelet declines were not clinically significant in most patients and were generally well managed with monitoring and dose adjustment. Some patients discontinued participation in the APPROACH study due to other non-serious adverse events, including sweating and chills, severe fatigue, rash and injection site reaction. In the APPROACH study and the open label extension study, the potentially treatment-related serious adverse events, or SAEs, observed were serious platelet events (grade 4 thrombocytopenia), which resolved without complication after cessation of dosing. Enhanced monitoring was implemented during the study to support early detection and management of these issues. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. In the COMPASS study, the most common adverse event in the volanesorsen-treated group of patients was injection site reactions, which were mostly mild, and a potentially treatment-related SAE of serum sickness reaction, from which the patient fully recovered. There have been no deaths and no treatment-related bleeding or cardiovascular events in any volanesorsen clinical study.

Akcea and we continue to conduct the BROADEN study, a Phase 3 clinical trial in patients with FPL, which continues to enroll, with data expected in 2019.

An open-label extension study is ongoing for patients with FCS who have completed or meet the study criteria for the APPROACH and COMPASS studies. Patients in the BROADEN study are also eligible to roll over into an open-label extension study upon completing dosing in the pivotal study.

Volanesorsen for the treatment of FCS is currently under regulatory review for marketing authorization in the U.S., EU and Canada. Volanesorsen has a PDUFA date of August 30, 2018 and an advisory committee meeting is scheduled for May 10, 2018. Volanesorsen has been granted priority review in Canada and a Promising Innovative Medicine, or PIM, designation by the United Kingdom's Medicines and Healthcare Products Regulatory Agency, or MHRA. The U.S. and European regulatory agencies have granted Orphan Drug Designation to volanesorsen for the treatment of people with FCS. The European regulatory agency has also granted Orphan Drug Designation to volanesorsen for the treatment of FPL. In addition, Akcea and we have an ongoing OLE study of volanesorsen in people with FCS, in which all patients are treated with volanesorsen. Akcea and we also opened an EAP for eligible patients. Our EAP program is being initiated on a country-by-country basis globally and is currently available in select countries in Europe.

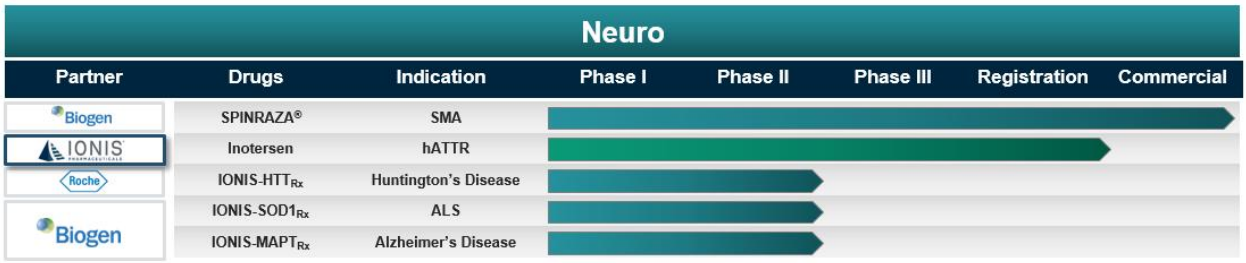
Akcea plans to globally commercialize volanesorsen for both FCS and FPL, if approved.

See our separate section below where we further discuss Akcea, our commercial affiliate.

Neurological Disease Franchise

We are discovering and developing antisense drugs to treat people with inadequate treatment options for both rare and common neurological diseases. According to the National Institute of Neurological Disorders and Stroke, or NINDS, at the National Institutes of Health, or NIH, a third of the 7,000 known rare diseases are neurological disorders or thought to include a neurological component.

Ionis Neurological Disease Pipeline



SPINRAZA – See the drug description under "Our Marketed Drug" section above.

Inotersen – See the drug description under "Our Drugs Under Regulatory Review for Marketing Authorization" section above.

IONIS-HTT$_{Rx}$ – IONIS-HTT$_{Rx}$ is a Generation 2+ antisense drug we designed to target the underlying cause of HD by reducing the production of the toxic mHTT protein. We and Roche entered into a collaboration to develop and commercialize antisense drugs to treat HD in April 2013. Roche licensed IONIS-HTT$_{Rx}$ from us in December 2017. Roche is now responsible for all IONIS-HTT$_{Rx}$ development, regulatory and commercialization activities and costs, including managing the ongoing OLE and all future studies.

HD is a rare, inherited, genetic brain disorder that results in the progressive deterioration of mental abilities and physical control. In the U.S., there are approximately 30,000 individuals with symptomatic HD and more than 200,000 people at risk of inheriting HD. HD is a triplet repeat disorder and is one of a large family of genetic diseases in which the body mistakenly repeats certain gene sequences. The resulting mHTT protein is toxic and gradually damages neurons in the brain. Symptoms of HD usually appear between the ages of 30 to 50 years and continually worsen over a 10 to 25-year period. Ultimately, the weakened individual succumbs to pneumonia, heart failure or other complications. Presently, there is no effective disease-modifying treatment, and current approaches only focus on managing the severity of some disease symptoms.

In December 2017, we announced that we had completed a randomized, placebo-controlled, dose escalation, Phase 1/2a clinical study of IONIS-HTT$_{Rx}$ in patients with early stage HD. Dose-dependent reductions of mHTT were observed among patients treated with IONIS-HTT$_{Rx}$, with a safety and tolerability profile supporting continued development.

The FDA and EMA have granted Orphan Drug Designation for IONIS-HTT$_{Rx}$ to treat people with HD.

IONIS-SOD1$_{Rx}$ – IONIS-SOD1$_{Rx}$ is a Generation 2+ antisense drug we designed to reduce the production of superoxide dismutase 1, or SOD1, which is the best understood genetic cause of familial amyotrophic lateral sclerosis, or ALS. We are collaborating with Biogen to develop IONIS-SOD1$_{Rx}$ to treat people with an inherited form of ALS, SOD1-ALS.

ALS is a rare, fatal, neurodegenerative disorder. People with ALS suffer progressive degeneration of the motor neurons, which results in a declining quality of life and ultimately death. The second most common familial form of ALS is SOD1-ALS, in which people have a mutation in the SOD1 gene that causes a progressive loss of motor neurons. As a result, people with SOD1-ALS experience muscle weakness, loss of movement, difficulty in breathing and swallowing and eventually succumb to their disease. Currently, treatment options for people with ALS are extremely limited with no drugs that significantly slow disease progression.

Biogen is evaluating IONIS-SOD1$_{Rx}$ in a randomized, placebo-controlled, dose escalation, Phase 1/2 clinical study in patients with ALS, including patients with SOD1-ALS.

IONIS-MAPT$_{Rx}$ – IONIS-MAPT$_{Rx}$ is a Generation 2+ antisense drug designed to selectively reduce production of the 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 frontotemporal dementia, or FTD.

Microtubule-associated protein tau, or MAPT, or tau, is thought to be a contributor or cause of certain neurodegenerative diseases, known as tauopathies, that are characterized by the deposition of abnormal tau protein in neurons and glia in the brain. These disorders include AD, Progressive Supranuclear Palsy, or PSP, and some forms of FTD.

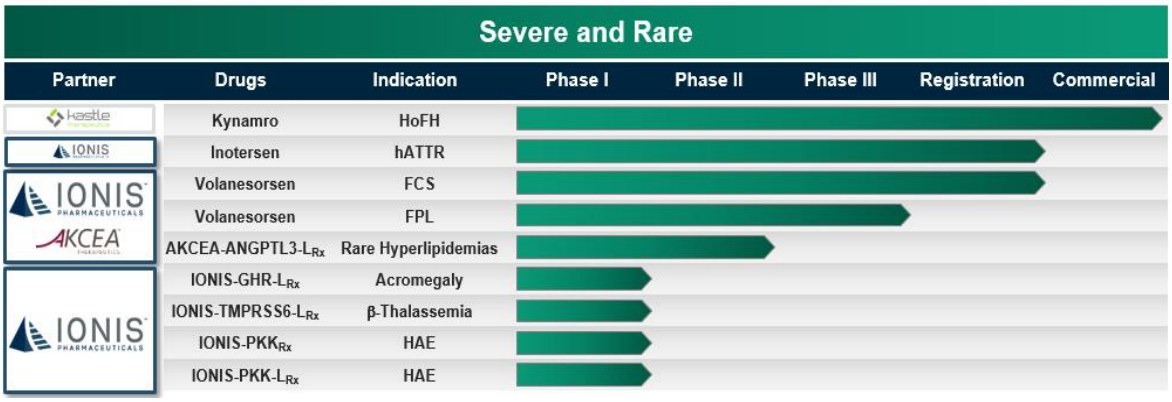
We and Biogen are evaluating IONIS-MAPT$_{Rx}$ in a Phase 1/2a, randomized, placebo-controlled, dose-escalation study to evaluate the safety and activity of once-monthly intrathecal injections in patients with mild AD.

Severe and Rare Disease Franchise

Our severe and rare disease franchise is the largest franchise in our pipeline. We are discovering and developing antisense drugs to treat people with severe and rare diseases who need new treatment options. We believe our antisense technology could offer effective therapies for these people. According to the NIH there are approximately 5,000 to 8,000 rare diseases, many life-threatening or fatal. Unfortunately, people with many of these severe and rare diseases have few effective therapies available. Since most of these diseases are genetic or have a genetic component, parents often pass the disease to their children, creating a legacy of the disease resulting in profound effects on the family.

Due to the severe nature of these diseases and the lack of available treatments, there is an opportunity for more flexible and efficient development paths to the market. This means that, in some cases, the studies necessary for us to demonstrate proof-of-concept with a particular drug may also be the studies that complete our marketing registration package, thereby providing us with a relatively rapid path to market for potential new treatments for these devastating and often fatal diseases. For example, SPINRAZA was approved five years after we began the Phase 1 study for it.

IONIS' Severe and Rare Disease Pipeline



Kynamro – Kynamro (mipomersen sodium) injection is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated as an adjunct to lipid-lowering medications and diet, to reduce low density lipoprotein-cholesterol, or LDL-C, apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol in patients with homozygous familial hypercholesterolemia, or HoFH. Kynamro is approved for use in people with HoFH in the U.S. and several other countries. In 2016 Kastle acquired the global rights to develop and commercialize Kynamro and also began marketing and selling Kynamro.

Inotersen – See the drug description under "Our Drugs Under Regulatory Review for Marketing Authorization" section above.

Volanesorsen – See the drug description under "Our Drugs Under Regulatory Review for Marketing Authorization" section above.

AKCEA-ANGPTL3-L$_{Rx}$ – See the drug description under the "Akcea Therapeutics" section below.

IONIS-GHR-L_{Rx} – IONIS-GHR-L_{Rx} is a LICA drug we designed to reduce the production of the growth hormone receptor, or GHr, to decrease the circulating level of insulin-like growth factor-1, or IGF-1. IGF-1 is a hormone primarily produced in the liver that plays an important role in childhood growth and has anabolic effects in adults. Several different diseases result from abnormally low or high levels of IGF-1, or an inappropriate response to this hormone. When produced in excess, IGF-1 results in acromegaly, a chronic, slowly progressing and life-threatening disease.

We have completed a Phase 1, double-blind, placebo-controlled, dose-escalation study of IONIS-GHR-L_{Rx} in healthy volunteers. Results from the Phase 1 study demonstrated an acceptable safety profile supportive of continued development.

IONIS-TMPRSS6-L_{Rx} – IONIS-TMPRSS6-L_{Rx} is a LICA drug we designed to reduce 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 plays an important role in the regulation of the body's iron homeostasis through the control of the iron regulatory protein hepcidin. Inhibition of TMPRSS6 leads to increased production of hepcidin, which results in more effective red blood cell production in the bone marrow and reduced iron toxicity in the liver as a result of improved control of iron availability. Results from preclinical and clinical studies suggest that reducing levels of TMPRSS6 may be an effective strategy to control iron availability, improve liver iron toxicity and increase red blood cell production under conditions of β-thalassemia.

We are currently evaluating IONIS-TMPRSS6-L_{Rx} in a randomized, double-blind, placebo-controlled, dose-escalation Phase 1 study in healthy volunteers.

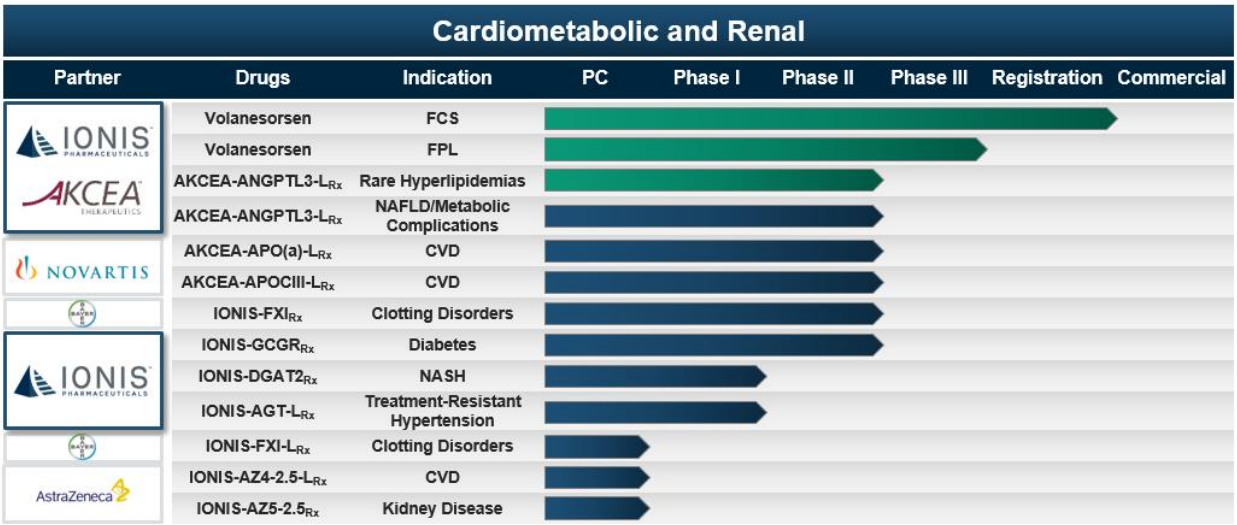
IONIS-PKK_{Rx} and IONIS-PKK-L_{Rx} – IONIS-PKK_{Rx} and IONIS-PKK-L_{Rx} are antisense drugs we designed to reduce the production of prekallikrein, or PKK, to treat people with hereditary angioedema, or HAE. HAE is a rare genetic disease that is characterized by rapid and painful attacks of inflammation 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_{Rx} and IONIS-PKK-L_{Rx} could be effective prophylactic approaches to preventing HAE attacks. In patients with frequent or severe attacks, doctors may use prophylactic treatment approaches to prevent or reduce the severity of HAE attacks. However, current prophylactic treatment approaches are very limited and have major tolerability issues due to challenging administration requirements leaving patients with few therapeutic options.

We have completed a Phase 1 study evaluating IONIS-PKK_{Rx} in healthy volunteers and we are exploring potential development options. We are currently evaluating IONIS-PKK-L_{Rx} in a Phase 1, randomized, double-blind, placebo-controlled, dose-escalation study in healthy volunteers. The Phase 1 study is evaluating single and multiple doses of IONIS-PKK-L_{Rx} administered subcutaneously.

Cardiometabolic and Renal Disease Franchise

Cardiovascular disease, or CVD, is an important area of focus for us. According to the World Health Organization, or WHO, cardiovascular disease was the number 1 cause of death globally. An estimated 17.7 million people died from CVDs in 2015, representing 31 percent of all global deaths. The drugs in our cardiovascular franchise target the key components of cardiovascular disease, including various atherogenic lipids, inflammation and thrombosis. Metabolic disorders are chronic diseases that affect millions of people. There is a significant need for new therapies for these people. According to the Centers for Disease Control and Prevention, diabetes affects more than 29 million people in the U.S., or nine percent of the population, with type 2 diabetes constituting 90 to 95 percent of those cases.

IONIS' Cardiometabolic and Renal Disease Pipeline



Volanesorsen – See the drug description under "Our Drugs Under Regulatory Review for Marketing Authorization" section below.

AKCEA-ANGPTL3-L$_{Rx}$ – See the drug description under the "Akcea Therapeutics" section below.

AKCEA-APO(a)-L$_{Rx}$, – See the drug description under the "Akcea Therapeutics" section below.

AKCEA-APOCIII-L$_{Rx}$ – See the drug description under the "Akcea Therapeutics" section below.

IONIS-FXI$_{Rx}$ – IONIS-FXI$_{Rx}$ is a Generation 2+ antisense drug we designed to reduce 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, which is the formation of a blood clot inside blood vessels. Thrombosis 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. Given the mechanism of Factor XI inhibition, we believe that our drug has the potential to be used broadly as an anti-thrombotic in many different therapeutic settings for which additional safe and well tolerated anti-thrombotic drugs are needed.

We completed a Phase 2 open-label, comparator-controlled global study evaluating IONIS-FXI$_{Rx}$ in people undergoing total knee replacement surgery. The study compared the safety and activity of IONIS-FXI$_{Rx}$ to enoxaparin. In this study patients treated with 300 mg of IONIS-FXI$_{Rx}$ experienced a seven-fold lower rate of venous thromboembolic events, such as blood clots in a deep vein or in a lung, compared to those patients treated with enoxaparin. The data from this study were published in the New England Journal of Medicine in December 2014. In May 2015, we exclusively licensed IONIS-FXI$_{Rx}$ to Bayer.

In November 2016, we completed a Phase 2 double-blinded, randomized, placebo-controlled study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis. In this Phase 2 study, patients treated with IONIS-FXI$_{Rx}$ achieved statistically significant, dose-dependent reductions in Factor XI activity. There were no clinically meaningful reductions in platelets and no treatment-related major or clinically relevant non-major bleeding events.

We are currently evaluating IONIS-FXI$_{Rx}$ in a Phase 2b study in approximately 200 people with end-stage renal disease on hemodialysis to finalize dose selection.

IONIS-GCGR$_{Rx}$ – IONIS-GCGR$_{Rx}$ is a Generation 2+ antisense drug we designed to reduce the production of glucagon receptors, or GCGR, to treat people 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. We are developing IONIS-GCGR$_{Rx}$ to provide better glucose control for people with type 2 diabetes. In people with advanced diabetes, uncontrolled glucagon action can lead to significant increases in blood glucose level. In addition, reducing GCGR produces more active glucagon-like peptide-1, or GLP-1, a hormone that preserves pancreatic function and enhances insulin secretion. We are developing IONIS-GCGR$_{Rx}$ with Suzhou Ribo Life Sciences Co., for the treatment of diabetes in China.

In January 2017, we reported results from a Phase 2 dose optimization study in which patients treated with IONIS-GCGR$_{Rx}$ achieved robust and sustained, statistically significant improvements in hemoglobin A1c, or HbA1c, and other measures of glucose control after 26 weeks of treatment. Additionally, IONIS-GCGR$_{Rx}$-treated patients experienced a mean increase in total GLP-1 from baseline compared to a decline in placebo-treated patients. The safety and tolerability profile of IONIS-GCGR$_{Rx}$ in the Phase 2 program supports continued development.

In March 2017, we licensed IONIS-GCGR$_{Rx}$ to Ribo to develop and commercialize the drug in China.

IONIS-DGAT2$_{Rx}$ – IONIS-DGAT2$_{Rx}$ is a Generation 2+ antisense drug we designed to reduce the production of DGAT2, or diacylglycerol acyltransferase 2, to treat people with nonalcoholic steatohepatitis, or NASH. NASH is a common liver disease characterized by excessive triglycerides in the liver with concurrent inflammation and cellular damage. As NASH progresses, scarring, or fibrosis, begins to accumulate in the liver. Ultimately, cirrhosis of the liver develops and the liver can no longer function normally. Currently, it is estimated that two to three percent of the general population have NASH. However, with the growing obesity epidemic, the number of people with NASH should also continue to rise. About 20 percent of people with NASH are reported to have a liver that does not function properly due to long-term damage, known as cirrhosis. Of those with NASH-related cirrhosis, 30 to 40 percent experience liver-related death. Currently, liver transplantation is the only treatment for advanced cirrhosis and liver failure. Because of the high prevalence of NASH, it has recently become the third most common indication for liver transplantation in the U.S.

DGAT2 is an enzyme that catalyzes the final step in triglyceride synthesis in the liver. Reducing the production of DGAT2 should therefore decrease triglyceride synthesis in the liver. In animal models of obesity and fatty liver disease, antisense inhibition of DGAT2 significantly improved non-alcoholic fatty liver disease, or NAFLD, lowered blood lipid levels and reversed diet-induced insulin resistance. NASH is a more severe form of NAFLD.

We are evaluating IONIS-DGAT2$_{Rx}$ in a Phase 2 randomized, placebo-controlled, dose-escalation study in patients with type 2 diabetes and NAFLD.

IONIS-AGT-L$_{Rx}$ – IONIS-AGT-L$_{Rx}$ is a LICA drug we designed to reduce the production of angiotensinogen to decrease blood pressure in people with treatment resistant hypertension, or TRH. Despite availability of generic antihypertensive agents, TRH is a major contributor to cardiovascular and renal disease.

We are evaluating IONIS-AGT-L$_{Rx}$ in a blinded, randomized, placebo-controlled, dose-escalation Phase 1/2a study in healthy volunteers.

Cancer Franchise and Other Drugs in Development

Cancer is an area of significant unmet medical need. Cancer is an extremely complex disease that involves a large number of targets. Using our antisense technology, we can validate multiple potential cancer targets from a variety of different cancers, and rapidly identify anti-cancer drugs, which in many cases are the same or similar sequences to those used to validate the target. We preferentially select anti-cancer targets that provide a multi-faceted approach to treating cancer.

Our cancer franchise consists of anti-cancer antisense drugs that act upon biological targets associated with cancer progression and/or treatment resistance. We have a strategic alliance with AstraZeneca, which includes an anti-cancer collaboration that expands our anti-cancer efforts and supports a robust clinical development plan for IONIS-STAT3-2.5$_{Rx}$ and IONIS-KRAS-2.5$_{Rx}$. AstraZeneca brings significant experience that enables the identification of novel genetic and epigenetic targets for cancer. Combining AstraZeneca's expertise with our drug discovery technology, we plan to expand our cancer franchise with a number of promising new anti-cancer targets. We also have a collaboration agreement with University of Texas MD Anderson Cancer Center to identify cancer targets and create novel antisense drugs to treat cancer together.

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

In addition to cancer programs, we continue to advance other drugs in development that are outside of our core therapeutic areas, such as IONIS-FB-L$_{Rx}$ for compliment-mediated diseases, and the antiviral drugs we and GSK are developing.

IONIS' Oncology/Other Pipeline

IONIS-STAT3-2.5$_{Rx}$ – IONIS-STAT3-2.5$_{Rx}$, also referred to as AZD9150, is a Generation 2.5 antisense drug we designed to reduce the production of signal transducer and activator of transcription 3, or STAT3, to treat people with cancer. STAT3 is a protein involved in the translation of key factors critical for tumor cell growth and survival. STAT3 is over-active in a variety of cancers, including brain, lung, breast, bone, liver and multiple myeloma. Physicians believe that overactivity in STAT3 prevents cancer cell death and promotes tumor cell growth. IONIS-STAT3-2.5$_{Rx}$ is a part of our collaboration with AstraZeneca to discover and develop anti-cancer drugs. We believe the significant potency we observed in our preclinical studies with IONIS-STAT3-2.5$_{Rx}$ broadens the therapeutic opportunities for IONIS-STAT3-2.5$_{Rx}$ into many different types of cancer in which STAT3 is implicated.

In September 2017, we and AstraZeneca announced data from a Phase 1b/2 study of IONIS-STAT3-2.5$_{Rx}$ in combination with Imfinzi (durvalumab), AstraZeneca's PD-L1 blocking antibody, in people with advanced solid tumors and recurrent metastatic head and neck cancer. The treatment combination demonstrated a 29 percent (8/28) objective response rate with four partial responses, or PR, and four complete responses, or CR, of which one was a CR in target lesions only. An additional eight people on the treatment combination had stable disease, or SD, at 12 weeks, resulting in an overall disease control rate of 57 percent (16/28). A complete response was seen in a person with recurrent/metastatic squamous cell carcinoma of the head and neck that was refractory to previous PD-L1 treatment. IONIS-STAT3-2.5$_{Rx}$ in combination with Imfinzi demonstrated a safety and tolerability profile supporting continued development.

IONIS-KRAS-2.5$_{Rx}$ - IONIS-KRAS-2.5$_{Rx}$, also referred to as AZD4785, is a Generation 2.5 antisense drug designed to selectively inhibit KRAS, one of the most frequently mutated genes in cancer. KRAS mutations are thought to underlie the pathogenesis of up to 30 percent of human tumors. The KRAS protein is involved in regulating cell division and tumor cell survival. IONIS-KRAS-2.5$_{Rx}$ is a part of our collaboration with AstraZeneca to discover and develop anti-cancer drugs.

AstraZeneca is evaluating IONIS-KRAS-2.5$_{Rx}$ in a Phase 1/2, open-label, multi-center, dose-escalation study in people with advanced solid tumors for whom KRAS may be an important driver of tumor survival.

IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ – IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ are antisense drugs we designed to reduce 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, which is present in both acute and chronic infections and is associated with a poor prognosis in people with chronic HBV infection. IONIS-HBV-L$_{Rx}$ is our first anti-infective drug in development that incorporates our LICA technology. Together with GSK, we are evaluating IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ to treat 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.

We and GSK are evaluating both IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ in Phase 2 studies in people with HBV infection.

IONIS-AR-2.5$_{Rx}$ – IONIS-AR-2.5$_{Rx}$ is a Generation 2.5 antisense drug 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 people diagnosed with metastatic prostate cancer, current treatments largely involve opposing the action of androgens by blocking the AR or removing circulating androgens. Although androgen deprivation therapy approaches are initially effective in delaying disease progression, people with metastatic prostate cancer will progress in their disease. 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, over expression and mutation of the AR gene. Because IONIS-AR-2.5$_{Rx}$ can inhibit the production of all known forms of AR, we believe that this drug has the potential to be useful in treating people with all stages of prostate cancer, including those who are resistant to current therapies.

AstraZeneca completed an open-label, dose-escalation, Phase 1/2 clinical study of IONIS-AR-2.5$_{Rx}$ in people with advanced tumors for which the androgen receptor pathway is potentially a contributing factor. The drug exhibited a good safety and tolerability profile supportive of continued development. In March 2017, we licensed IONIS-AR-2.5$_{Rx}$ to Ribo to develop and commercialize the drug in China.

IONIS-FB-L$_{Rx}$ - IONIS-FB-L$_{Rx}$ is a LICA drug we designed to reduce 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 overaction of this cascade has been associated with the development of several complement-mediated diseases, including dry age-related macular degeneration, or AMD. FB, which plays a pivotal role in this cascade, is produced predominately in the liver and circulates at high levels throughout the vascular system, including in capillaries in the eye.

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. The safety and tolerability profile of IONIS-FB-L$_{Rx}$ supports further clinical development.

We are currently evaluating IONIS-FB-L$_{Rx}$ in a Phase 2 study in people with dry AMD.

Preclinical Drugs in Development

The efficiency and broad applicability of our technology provides us with nearly unlimited targets against which to develop drugs. On average, it takes 12 to 18 months to complete the preclinical studies necessary to support clinical development. Over the last year we added eight new drugs to our preclinical pipeline.

IONIS' Preclinical Pipeline

Neuro

Drugs	Indication	Partner
IONIS-C9$_{Rx}$	ALS	Biogen
IONIS-BIIB6$_{Rx}$	Neurodegenerative Disease	Biogen
IONIS-BIIB7$_{Rx}$	Neurodegenerative Disease	Biogen
IONIS-BIIB8$_{Rx}$	Neurodegenerative Disease	Biogen

Severe and Rare

Drugs	Indication	Partner
IONIS-RHO-2.5$_{Rx}$	Autosomal Dominant Retinitis Pigmentosa	Ionis
IONIS-ENAC-2.5$_{Rx}$	Cystic Fibrosis	Ionis
IONIS-TTR-L$_{Rx}$	ATTR	Ionis

Cardiometabolic and Renal

Drugs	Indication	Partner
IONIS-AZ4-2.5-L$_{Rx}$	CVD	AstraZeneca
IONIS-AZ5-2.5$_{Rx}$	Kidney Disease	AstraZeneca
IONIS-FXI-L$_{Rx}$	Clotting Disorders	Bayer

Oncology

Drugs	Indication	Partner
IONIS-IRF4-2.5$_{Rx}$	Cancer	Ionis
IONIS-EZH2-2.5$_{Rx}$	Cancer	Ionis

Other

Drugs	Indication	Partner
IONIS-JBI1-2.5$_{Rx}$	GI Autoimmune Disease	Janssen
IONIS-JBI2-2.5$_{Rx}$	GI Autoimmune Disease	Janssen

Akcea Therapeutics: Our Affiliate Focused on Developing and Commercializing Drugs to Treat People with Serious Cardiometabolic Diseases Caused by Lipid Disorders

Akcea Therapeutics is our development and commercialization affiliate that we formed in late 2014 to focus on developing and commercializing drugs to treat people with serious cardiometabolic diseases caused by lipid disorders. As part of its formation, we granted Akcea exclusive rights to develop and commercialize volanesorsen, AKCEA-APO(a)-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-ANGPTL3-L_{Rx}. These four novel drugs are based on our antisense technology and have the potential to treat multiple indications. We describe each of these drugs in more detail below.

Akcea is assembling the global infrastructure to develop the drugs in its pipeline, to commercialize them with a focus on lipid specialists as the primary call point and to create the specialized support required to address rare disease patient populations. Akcea and we entered into a collaboration, option and license agreement with Novartis, in which Akcea granted Novartis an exclusive option to license AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Both these drugs have the potential to treat people who are at high cardiovascular risk due to inadequately treated lipid disorders. After Akcea completes the Phase 2 development of each of these drugs, Novartis has the option to license each drug. If Novartis licenses one or both drugs, it plans to, for each licensed drug, use commercially reasonable efforts to conduct, at its expense, a Phase 3 cardiovascular outcome study in a high-risk patient population and will be responsible for the worldwide development and commercialization activities. Novartis brings significant resources and expertise that should support the development and commercialization of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} for significant high-risk patient populations. Akcea also plans to co-commercialize any such drug through its specialized sales force focused on lipid specialists in selected markets.

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

Volanesorsen – Volanesorsen is a Generation 2+ antisense drug under regulatory review for marketing authorization in the U.S., EU and Canada for the treatment of people with FCS. Akcea and we are also developing volanesorsen to treat people with FPL. For more information on the regulatory and development plan for volanesorsen, see the drug description under "Our Drugs under Regulatory Review for Marketing Authorization" section above.

AKCEA-APO(a)-L_{Rx} – AKCEA-APO(a)-L_{Rx} is a LICA drug we designed to reduce the production of apolipoprotein(a), or Apo(a), protein in the liver to offer a direct approach for reducing lipoprotein(a), or Lp(a). Lp(a) is an independent risk factor for CVD that is composed of an apolipoprotein(a) protein bound to an LDL-cholesterol particle. Akcea initiated a collaboration with Novartis in January 2017 to advance AKCEA-APO(a)-L_{Rx}.

Akcea is developing AKCEA-APO(a)-L_{Rx} for people who are at significant risk of CVD because of their elevated levels of Lp(a). AKCEA-APO(a)-L_{Rx} inhibits the production of the Apo(a) protein, thereby reducing Lp(a). Lp(a) is a very atherogenic and thrombogenic form of LDL. Elevated Lp(a) is recognized as an independent, genetic cause of coronary artery disease, heart attack, stroke and peripheral arterial disease. 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 60 mg/dL.

Lp(a) is difficult to inhibit using other technologies, such as small molecules and antibodies; there are multiple genetically-determined forms of the Apo(a) molecule and creating a small molecule or antibody that can interact with multiple targets is difficult. We believe antisense technology is particularly well suited to address hyperlipoproteinemia(a) because it specifically targets the RNA that codes for all forms of the Apo(a) molecule. As a result, it can stop the production of all the forms of the protein. Furthermore, we believe addressing elevated Lp(a) is the next important horizon in lipid-focused treatment and, through Akcea's collaboration with Novartis, it plans to develop AKCEA-APO(a)-L_{Rx} to treat people with established cardiovascular disease in whom hyperlipoproteinemia(a) likely plays a causal role.

Akcea and we completed a Phase 1/2a study with AKCEA-APO(a)-L_{Rx} in patients with hyperlipoproteinemia(a) and reported results at the American Heart Association, or AHA, annual meeting in November 2015. In this clinical study, we observed significant and sustained reductions in Lp(a) of up to 97 percent with a mean reduction of 79 percent after only a single, small volume dose of AKCEA-APO(a)-L_{Rx}. With multiple doses of AKCEA-APO(a)-L_{Rx}, we observed even greater reductions of Lp(a) of up to 99 percent with a mean reduction of 92 percent. Based on these results, Akcea started a Phase 2b dose-ranging study of AKCEA-APO(a)-L_{Rx} in patients with hyperlipoproteinemia(a) and established CVD. Akcea completed enrollment in this study in January 2018 and expects to report data from this study in the second half of 2018.

AKCEA-ANGPTL3-L_{Rx} – AKCEA-ANGPTL3-L_{Rx} is a LICA drug we designed to reduce the production of the angiopoietin-like 3, or ANGPTL3, protein. Akcea and we are developing AKCEA-ANGPTL3-L_{Rx} to treat multiple lipid disorders.

People with elevated levels of the angiopoietin-like 3, or ANGPTL3, protein have high LDL-C and triglyceride levels. Studies show this elevation is associated with an increased risk of premature heart attacks, increased arterial wall thickness, increased liver fat and multiple metabolic disorders, such as insulin resistance. 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, an analog of AKCEA-ANGPTL3-L_{Rx} inhibited the production of the ANGPTL3 protein in the liver, resulting in lower liver fat accumulation and lower blood levels of LDL-C, triglycerides and very low density lipoprotein cholesterol, or VLDL-C. In addition, our preclinical data and initial Phase 1 data suggest that inhibiting the production of ANGPTL3 could improve other lipid parameters, including triglyceride levels and total cholesterol, as well as metabolic parameters, such as insulin sensitivity.

We and Akcea have completed a Phase 1/2 program for AKCEA-ANGPTL3-L_{Rx} in patients with elevated triglycerides. We and Akcea reported results for the initial cohort from this study at the AHA meeting in November 2016 and published the data in the New England Journal of Medicine. In the fourth quarter of 2017, we and Akcea initiated a study of AKCEA-ANGPTL3-L_{Rx} in patients with nonalcoholic fatty liver disease, or NAFLD, with metabolic complications, which include hypertriglyceridemia, type 2 diabetes or nonalcoholic steatohepatitis, or NASH. We expect data from this study in 2019. Further, in the fourth quarter of 2017, we and Akcea initiated a study of AKCEA-ANGPTL3-L_{Rx} in patients with rare hyperlipidemias, including patients with FCS. If we and Akcea find that AKCEA-ANGPTL3-L_{Rx} can effectively lower triglyceride levels in patients with rare hyperlipidemias, including patients with FCS, through a different mechanism of action from volanesorsen, it may represent an opportunity to expand our FCS franchise. As part of our exploratory rare hyperlipidemia clinical program, we and Akcea are also studying AKCEA-ANGPTL3-L_{Rx} in patients with FPL and in patients with HoFH. Additional potential indications for which we may consider developing AKCEA-ANGPTL3-L_{Rx} include other rare hyperlipidemias and lipodystrophies.

AKCEA-APOCIII-L_{Rx} – is a LICA drug we designed to inhibit the production of apoC-III, the same protein inhibited by volanesorsen, for the broad population of people who are at risk for cardiometabolic disease due to their elevated triglyceride levels. Akcea and we initiated a collaboration with Novartis in January 2017 to advance AKCEA-APOCIII-L_{Rx}.

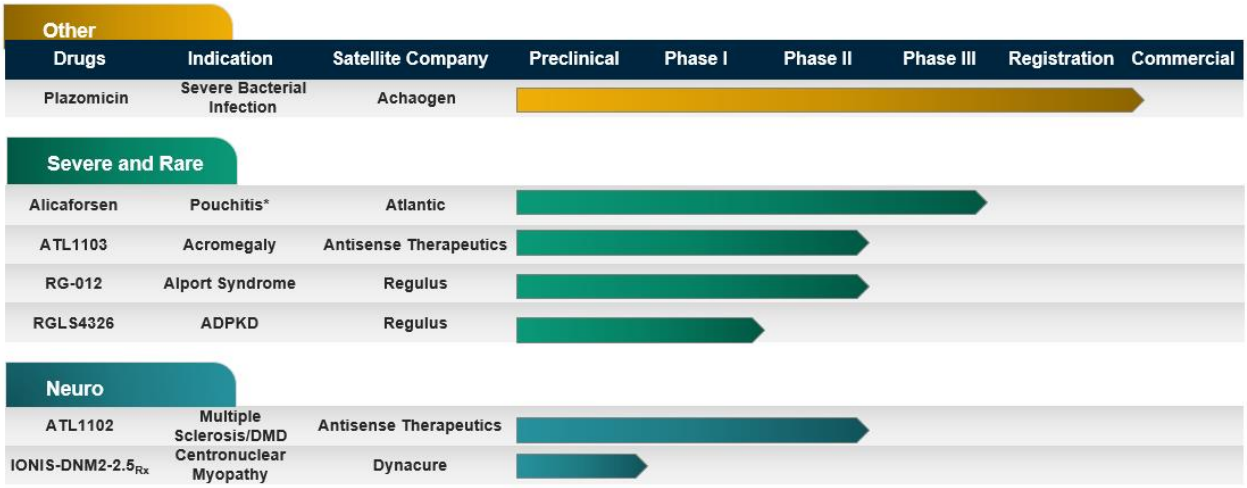
ApoC-III impacts triglyceride levels and may also increase inflammatory processes. This combination of effects makes apoC-III a promising target for people with LDL-C already controlled on statin therapy, but for whom triglycerides remain poorly controlled. We believe that the enhancements offered by our LICA technology can provide greater patient convenience by allowing for significantly lower doses and less frequent administration, compared to volanesorsen. We and Akcea conducted a Phase 1/2 study of AKCEA-APOCIII-L_{Rx} in people with elevated triglycerides and reported results from this study in the fourth quarter of 2017.

Under our and Akcea's collaboration with Novartis, we intend to complete the Phase 2 program required to define the appropriate dose and regimen to support a planned cardiovascular outcome study. We and Akcea initiated a Phase 2b dose-ranging study of AKCEA-APOCIII-L_{Rx} in patients with hypertriglyceridemia and established CVD in the first quarter of 2018 and plan to report data from this study in 2019.

Satellite Company Drugs in Development

We have successfully developed novel drugs we designed to treat many different diseases. In therapeutic areas that are outside of our core areas of development, we have licensed our drugs to highly focused satellite companies that have the specific expertise and resources to continue developing the drugs. For our satellite company drugs, we refer to the drug by the partner's name or compound number, such as plazomicin or ATL1103. We have listed these drugs below in our Satellite Company pipeline.

IONIS' Satellite Company Pipeline



* Named Patient Supply (see below).

Plazomicin – Plazomicin is an aminoglycoside drug that Achaogen is developing for the treatment of multi-drug resistant gram-negative bacterial infections. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis used to treat serious bacterial infections. In 2006, we licensed our proprietary aminoglycoside program to Achaogen. Achaogen discovered plazomicin based on technology licensed from us. Achaogen conducted two Phase 3 studies for plazomicin, CARE and EPIC. In December 2016, Achaogen announced that it completed two Phase 3 studies of plazomicin. The EPIC trial met its primary endpoint in patients with complicated urinary tract infections. The CARE trial demonstrated reduction in mortality in patients with serious multi-drug resistant infection due to carbapenem-resistant Enterobacteriaceae, or CRE compared with colistin, one of the few remaining antibiotics for treatment of infections due to CRE. Plazomicin was well tolerated in both Phase 3 studies.

Achaogen submitted an NDA to the FDA for plazomicin for the treatment of complicated urinary tract infections, including kidney infections and bloodstream infections due to certain Enterobacteriaceae in people who have limited to no alternative treatment options. FDA granted the NDA Priority Review and set a target action date under the PDUFA date of June 25, 2018. Achaogen plans to submit a MAA to the EMA in 2018.

The FDA has granted Fast Track Status for the development and regulatory review of plazomicin to treat serious and life-threatening CRE infections. In addition, plazomicin has received Qualified Infectious Disease Product, or QIDP, designation from the FDA. The QIDP designation provides certain incentives for the development of new antibiotics, including priority review and an additional five years of market exclusivity.

Alicaforsen – Alicaforsen is an antisense drug we designed to reduce the production of intercellular adhesion molecule 1, or ICAM-1. Ulcerative colitis, or UC, is an inflammatory bowel disease of the colon, a part of the large intestine, and pouchitis is an inflammation of the surgically constructed internal pouch created in people with UC who have had their diseased colons removed. In 2007, we licensed alicaforsen to Atlantic Pharmaceuticals for pouchitis, UC and other inflammatory diseases. Atlantic Pharmaceuticals is developing alicaforsen for the treatment of UC and currently supplies alicaforsen in response to physicians' requests under international Named Patient Supply regulations for people with inflammatory bowel disease. In 2017, under a rolling submission agreement with the FDA, Atlantic Pharmaceuticals filed the nonclinical data package of its NDA for alicaforsen to treat pouchitis. Alicaforsen has also been granted FDA Fast-Track designation, plus U.S. and European Orphan Drug designations for this indication.

ATL1103 – ATL1103 is an antisense drug we designed to reduce the production of the growth hormone receptor, or GHr, to treat people with acromegaly. Acromegaly is a serious, chronic, life-threatening disease triggered by excess secretion of GHr by benign pituitary tumors. In 2001, we licensed ATL1103 to Antisense Therapeutics Limited, or ATL. ATL conducted a successful Phase II trial of ATL1103 with the trial having met its primary efficacy endpoint by showing a statistically significant average reduction in sIGF-1 levels. ATL has also completed a high dose study of ATL1103 in adults with acromegaly in Australia.

RG-012 – RG-012 is an anti-miR, or an antisense oligonucleotide inhibitor of microRNA, targeting microRNA-21, or miR-21, to treat people with Alport syndrome, a life-threatening genetic kidney disease with no approved therapy. While there is little known information on the progression of this disease, researchers believe that miR-21 plays a critical role due to the observed increased miR-21 levels in animal models of Alport syndrome and in people with chronic kidney disease. Regulus is developing RG-012 in a strategic alliance with Genzyme, a Sanofi company, to treat Alport syndrome. In September 2017, Regulus initiated HERA, the Phase 2 randomized, double-blinded, placebo-controlled study evaluating the safety and efficacy of RG-012 in people with Alport syndrome.

RGLS4326 – RGLS4326 is an anti-miR, or an antisense oligonucleotide inhibitor of microRNA, designed to inhibit miR-17 to treat people with autosomal dominant polycystic kidney disease, or ADPKD, using a unique chemistry design to preferentially target the kidney. ADPKD, caused by the mutations in the PKD1 or PKD2 genes, is among the most common human monogenetic disorders and a leading genetic cause of end-stage renal disease. Approximately 1 in 1,000 people bear a mutation in either PKD1 or PKD2 genes worldwide. Preclinical studies with RGLS4326 have demonstrated a reduction in kidney cyst formation, improved kidney weight/body weight ratio, decreased cyst cell proliferation, and preserved kidney function in mouse models of ADPKD.

RGLS4326 is being studied in a Phase I randomized, double-blind, placebo-controlled, single ascending dose study designed to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of RGLS4326 administered subcutaneously in healthy volunteers.

ATL1102 – ATL1102 is an antisense drug we designed to reduce the production of CD49d, a sub-unit of Very Late Antigen-4, or VLA-4, for the treatment of people with multiple sclerosis, or MS. Results from preclinical studies demonstrated that inhibition of VLA-4 could positively affect a number of inflammatory diseases, including MS. In 2001, we licensed ATL1102 to ATL. ATL completed a chronic toxicology study in primates and a Phase 2a efficacy and safety trial. ATL1102 was shown by ATL to reduce MS lesions in the Phase 2a clinical trial and has also completed toxicology studies to support a potential future Phase 2b study in people with MS.

IONIS-DNM2-2.5$_{Rx}$ – IONIS-DNM2-2.5$_{Rx}$ is a Generation 2.5 antisense drug targeting dynamin 2 for the treatment of centronuclear myopathy, or CNM. CNM is a term for a group of rare, genetic, muscle disorders affecting children and young adults. These disorders are characterized by muscle weakness that can range from mild to profound. CNM, caused by mutations in the *DNM2* gene, is highly variable in presentation and severity, presenting at birth, during childhood or in adulthood. When *DNM2*-related CNM occurs during infancy or early childhood, common symptoms include reduced muscle strength, generalized weakness, facial and eye muscle weakness and paralysis of muscles surrounding the eye. Affected children may exhibit delays in attaining motor milestones, such as holding their head up. Facial weakness can cause infants to have a weak sucking ability and/or experience difficulties swallowing, potentially resulting in feeding difficulties. Eventually, affected individuals can develop breathing complications, and sometimes infection of the lungs causes death in early infancy.

IONIS-DNM2-2.5$_{Rx}$ is currently in IND-enabling preclinical studies.

Antisense Technology

Our antisense technology is an innovative platform for discovering first-in-class or best-in-class drugs for treating disease. We believe this technology represents an important advance in the way we treat disease. Unlike most other drug technologies that work by affecting existing proteins in the body, antisense drugs 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 only accessible to antisense technology.
- Precise specificity: we design antisense drugs to target a single RNA, which minimizes or eliminates the possibility our drugs will bind to unintended targets which can cause unwanted side effects.
- Good drug properties: antisense drugs distribute well throughout the body without the need for special formulations or vehicles. They also have a relatively long half-life of approximately two to four weeks in most tissues outside of the brain and spinal cord and three to four months in brain and spinal cord, which means patients and/or healthcare providers can dose our drugs weekly, monthly or even less frequently depending on the drug and target tissue.
- Ability to combine with other drugs: because antisense drugs do not interact with the enzymes that metabolize or break down other drugs, physicians can use our drugs in combination with other drugs.
- 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 drugs to potentially treat a wide range of diseases in a number of different therapeutic areas from severe and rare diseases to diseases that affect large patient populations. We focus our efforts on diseases in which there is a large unmet medical need with limited or no current treatments or in diseases for which we believe our drugs have a competitive advantage over existing therapies.

Technology Overview

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

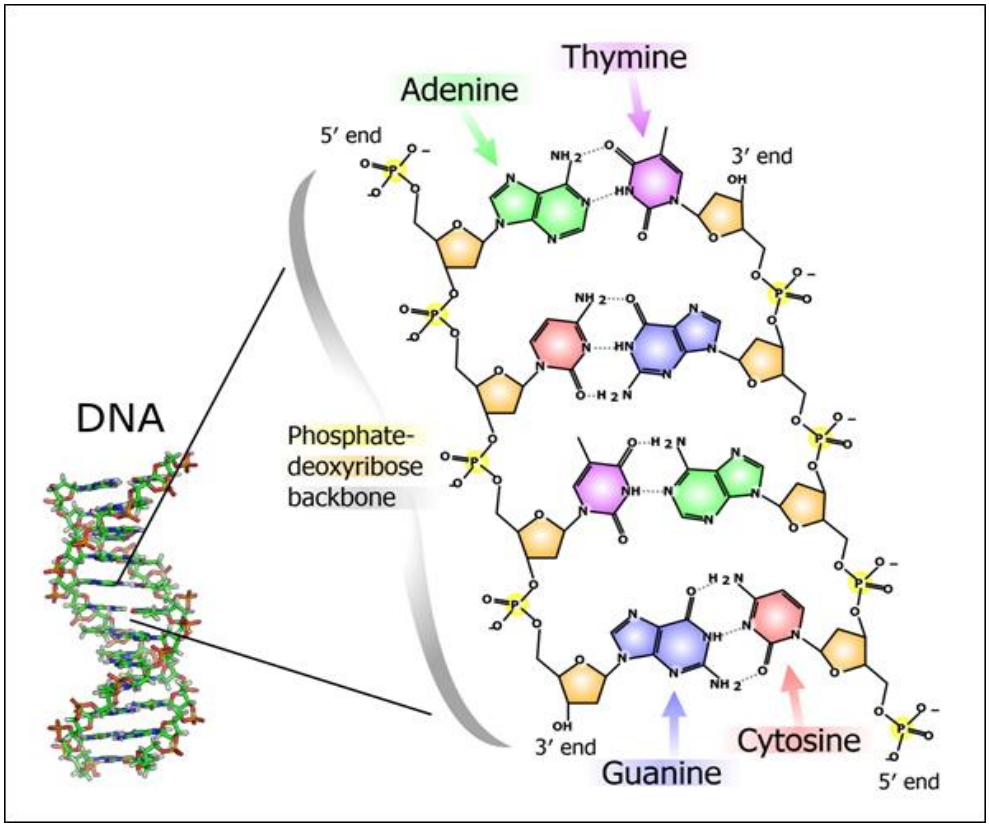


Figure 1: Illustration of DNA.

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

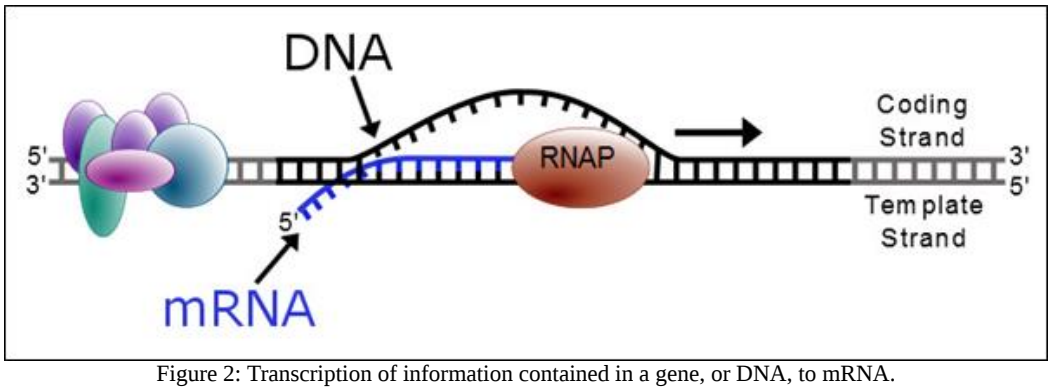


Figure 2: Transcription of information contained in a gene, or DNA, to mRNA.

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).

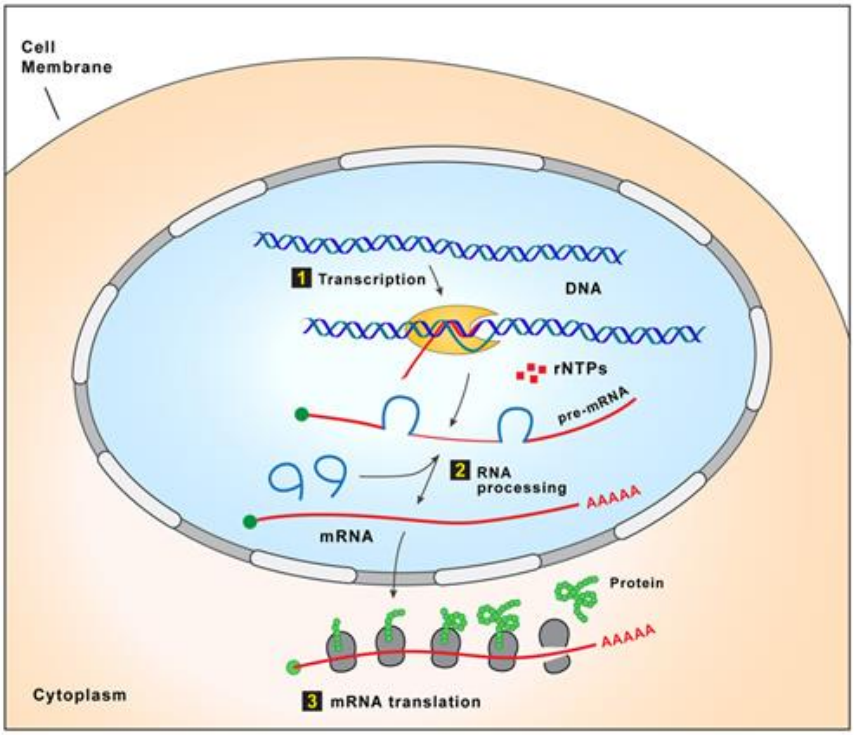


Figure 3: Translation of the protein-coding information contained in mRNA to protein.

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 drugs 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 drugs, which resemble DNA and RNA and are the complement of RNA. Our antisense drugs bind with high selectivity to the mRNA they were designed to target. Since each mRNA codes for a specific protein, this selectivity provides a level of specificity that is better than traditional drugs. As a result, we can design antisense drugs 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 drugs may be less toxic than traditional drugs because we can design them to minimize the impact on unintended targets.

We have developed the majority of the drugs in our pipeline using our advanced screens to produce drugs with what we believe have the best possible safety and tolerability profiles. We refer to our drugs that have passed these advanced screens as Generation 2+ drugs. We continue to advance our antisense technology to create even more potent drugs 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 drugs. These advancements provide us with greater opportunities to use our antisense drugs to treat a greater number of diseases and reach more patient populations. Today several of our early stage drugs and those entering our pipeline use our most advanced antisense technology, including our next generation chemistries, Generation 2.5, and our LICA technology.

Generation 2.5 chemistry is an Ionis advancement that we have demonstrated increases the potency of our drugs by up to ten-fold over our Generation 2+ drugs. This increase in potency enables our drugs to engage targets in a broader array of tissues. We have published data demonstrating that our Generation 2.5 drugs generally have enhanced potency over our Generation 2+ drugs and are broadly distributed throughout the body to multiple tissues including liver, kidney, lung, muscle, adipose, adrenal gland, peripheral nerves and tumor tissues. Our Generation 2.5 drugs constitute some of our recently added new drugs to our pipeline.

LICA (**LI**gand-**C**onjugated **A**ntisense) is a chemical technology we developed at Ionis that involves the attachment of 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 drugs with higher specificity to certain cell types that express these receptors relative to non-conjugated antisense drugs. We have demonstrated with multiple Generation 2+ LICA drugs that our LICA technology for liver targets can increase potency by up to more than thirty-fold over our non-LICA Generation 2+ drugs. We have also combined our LICA technology with our Generation 2.5 chemistry drugs to further increase potency. Although we designed our first LICA drugs to inhibit targets in the liver, we are also developing LICA conjugation technology that we can use to target other tissues and initial results are promising.

Antisense Targets and Mechanisms

There are more than a dozen different antisense mechanisms that we can exploit with our antisense technology. The majority of the drugs 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. We have also recently published research showing that we can use our proprietary oligonucleotide technology with CRISPR/Cas9, a gene editing system that uses RNA to activate, target and edit specific sites on DNA. Our work in this area provides an important step toward development of potential therapeutic applications for CRISPR technology.

When using antisense technology to inhibit the production of disease-causing proteins or reduce levels of harmful RNAs, our antisense drugs 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 drug 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 clinical development stage antisense drugs that use the RNase H1 mechanism to reduce disease protein production include, volanesorsen, inotersen, IONIS-FXI$_{Rx}$, IONIS-FXI-L$_{Rx,}$ AKCEA-APO(a)-L$_{Rx}$, IONIS-HTT$_{Rx}$, and others.

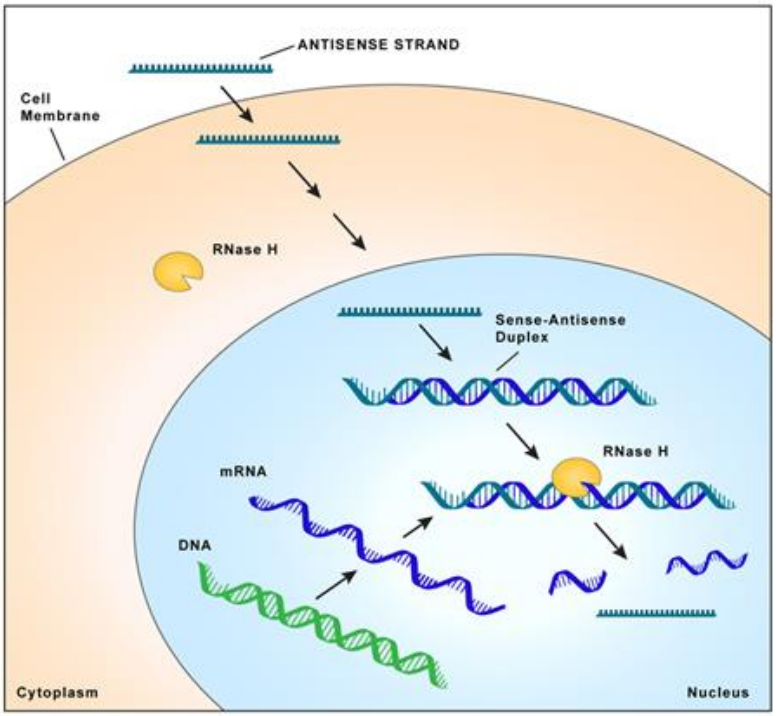


Figure 4: Antisense drug using the RNase H mechanism of action.

SPINRAZA is an example of an antisense drug 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.

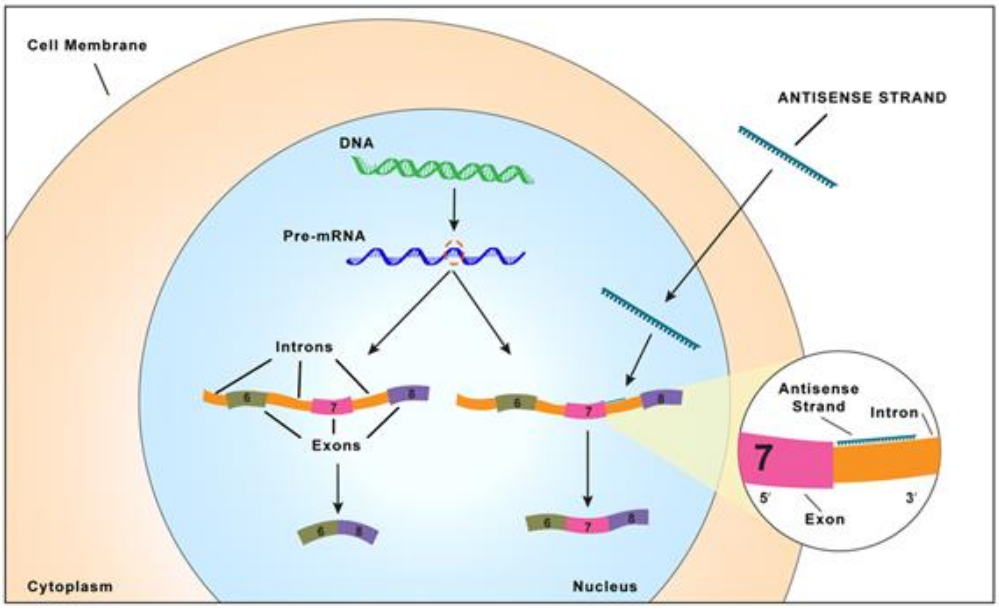


Figure 5: Antisense drug altering splicing of the SMN2 mRNA.

Another class of RNA targets for our antisense technology are microRNAs. To date, scientists have identified more than 700 microRNAs in the human genome, and have shown that the absence or presence of specific microRNAs in various cells is associated with specific human diseases, including cancer, viral infection, metabolic disorders and inflammatory disease. To fully exploit the therapeutic opportunities of targeting microRNAs, we co-founded Regulus Therapeutics as a company focused on the discovery, development and commercialization of microRNA-based therapeutics.

We are also making progress in designing antisense drugs 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 an 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 an antisense drugs for the treatment of AS.

Because the efficiency of our core technology platform can support multiple target-based antisense research programs without significantly increasing costs, we can develop antisense drugs to target a broad range of diseases, efficiently producing a large and broad proprietary portfolio of drugs. We are currently pursuing antisense drug discovery programs focused on various severe and rare diseases, cardiometabolic diseases, neurologic diseases, cancer and other diseases.

Collaborative Arrangements and Licensing Agreements

Partnering Strategy

We have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our drugs, advancing our technology, preparing to commercialize our drugs and selling our drugs. Our partners include the following companies, among others: AstraZeneca, Biogen, Bayer, GSK, Janssen, Novartis and Roche. Our partners bring resources and expertise that augment and build upon our internal capabilities. The depth of our knowledge and expertise with antisense technology together with our strong financial position provides us the flexibility to partner our drugs at what we believe is the optimal time to maximize the near- and long-term value of our drugs. We have distinct partnering strategies that we employ based on the specific program, therapeutic area and the expertise and resources our potential partners may bring to the collaboration.

- We have strategic partnerships through which we can broadly expand our drug discovery efforts to new disease targets in specific therapeutic areas. Our partners provide expertise, tools and resources to complement our drug discovery efforts. For instance, we established a broad strategic alliance with Biogen that pairs Biogen's extensive resources and expertise in neurodegenerative diseases with our antisense technology. Together we are creating a franchise of novel drugs for neurodegenerative diseases that has the potential to expand both our pipeline and Biogen's pipeline with promising new drugs. Most recently, we entered into a new collaboration agreement with Biogen to identify new antisense drugs for the treatment of SMA.

- We have partnerships with companies that bring significant expertise and global resources to develop and potentially commercialize drugs for a particular therapeutic area. For example, in January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. As a leader in the cardiovascular disease space, Novartis brings significant resources and expertise that should support the development and commercialization of these two drugs for significant high-risk patient populations. The collaboration with Novartis should enable us to accelerate the development of these drugs for broader patient populations as Novartis plans to conduct a cardiovascular outcome study for each of these drugs.

- We also form early stage research and development partnerships that allow us to expand the application of our technology to new therapeutic areas. For example, we established a collaboration with Janssen in December 2014, which brings together our RNA-targeted technology platform and Janssen's expertise in autoimmune disorders and therapeutic formulation to discover and develop antisense drugs to treat autoimmune disorders in the GI tract. Thus far, Janssen has licensed two drugs under our collaboration.

- We also work with a consortium of companies that can exploit our drugs and technologies outside our primary areas of focus. We refer to these companies as satellite companies. Through our satellite company collaborations, we expand the reach and potential of RNA-targeting therapeutics into disease areas that are outside of our core focus. For example, in October 2017, Achaogen submitted an NDA to the FDA for plazomicin. Plazomicin is an aminoglycoside Achaogen discovered based on the technology we licensed to Achaogen and we are eligible to earn milestone payments and royalties under our licensing agreement.

Financial Impact of Our Partnerships

Through our partnerships, we have created a broad and sustaining base of R&D revenue in the form of license fees, upfront payments and milestone payments while spending prudently to advance our pipeline and technology. Since 2007, we have received more than $2.4 billion in cash from upfront and licensing fees, equity purchase payments, milestone payments and research and development funding from our partnerships. We have the potential to earn over $13 billion in future milestone payments, licensing fees and other payments from our current partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through royalty arrangements. For example, during 2017 we earned $112.5 million in commercial revenue from SPINRAZA sales, adding a significant revenue stream to our broad base of R&D revenue.

Strategic Partnerships

AstraZeneca

Cardiometabolic and Renal Diseases Collaboration

In July 2015, we and AstraZeneca formed a strategic collaboration to discover and develop antisense therapies for treating cardiovascular and metabolic diseases primarily focused on targets in the kidney, and renal diseases. As part of the agreement, we granted AstraZeneca an exclusive license to IONIS-AZ4-2.5-L_{Rx}, a drug we designed to treat cardiovascular disease and our first drug that combines our Generation 2.5 and LICA technology. We also granted AstraZeneca the option to license a drug for each additional target advanced under this research collaboration. In February 2018, AstraZeneca licensed a second drug under our collaboration, IONIS-AZ5-2.5$_{Rx}$, a drug we designed to treat a genetically associated form of kidney disease. AstraZeneca is responsible for all further global development, regulatory and commercialization activities and costs for IONIS-AZ4-2.5-L_{Rx} and IONIS-AZ5-2.5$_{Rx}$ and any other future drug development candidates AstraZeneca accepts.

Under the terms of the agreement, we received a $65 million upfront payment. We are eligible to receive license fees and milestone payments of up to more than $4 billion as drugs under this collaboration advance. In addition, we are eligible to receive tiered royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. From inception through February 2018, we have generated over $120 million in payments under this collaboration, including $30 million when AstraZeneca licensed IONIS-AZ5-2.5$_{Rx}$ in February 2018.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense drugs to treat cancer. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize IONIS-STAT3-2.5$_{Rx}$ for the treatment of cancer and an option to license up to three anti-cancer drugs under separate research programs. AstraZeneca is responsible for all global development, regulatory and commercialization activities for IONIS-STAT3-2.5$_{Rx}$. We and AstraZeneca have evaluated IONIS-STAT3-2.5$_{Rx}$ in people with advanced metastatic hepatocellular carcinoma and advanced lymphoma. AstraZeneca is evaluating IONIS-STAT3-2.5$_{Rx}$ in combination with Imfinzi (durvalumab), AstraZeneca's anti-PD-L1 drug, in people with head and neck cancer and in people with diffuse large B cell lymphoma. Under the research program, we are responsible for identifying a development candidate for each of the three anti-cancer research programs. AstraZeneca has the option to license drugs resulting from each of the three anti-cancer research programs, and if AstraZeneca exercises its option for a drug, it will be responsible for all further global development, regulatory and commercialization activities and costs for such drug. The first development candidate identified under the anti-cancer research program was IONIS-KRAS-2.5$_{Rx}$, which AstraZeneca licensed from us in December 2016. IONIS-KRAS-2.5$_{Rx}$ is a Generation 2.5 antisense drug we designed to directly target KRAS, one of the most frequently mutated genes in cancer.

Under the terms of the agreement, we received $31 million in upfront payments. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive tiered royalties up to the low to mid-teens on sales from any drugs resulting from these programs. If AstraZeneca successfully develops IONIS-STAT3-2.5$_{Rx}$, IONIS-KRAS-2.5$_{Rx}$ and two other drugs under the research program, we could receive license fees and milestone payments of up to more than $750 million. From inception through February 2018, we have generated more than $95 million in payments under this collaboration.

For additional details about our collaboration agreements with AstraZeneca, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

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 drugs with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved drug to treat people with SMA. Additionally, we and Biogen are currently developing six other drugs to treat neurodegenerative diseases under these collaborations, including IONIS-SOD1$_{Rx}$ for ALS, IONIS-MAPT$_{Rx}$ (formerly IONIS-BIIB4$_{Rx}$) for AD and IONIS-C9$_{Rx}$ (formerly IONIS-BIIB5$_{Rx}$) for ALS, IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ to treat undisclosed neurodegenerative diseases. In addition to these drugs, we and Biogen are evaluating numerous additional targets to develop drugs to treat neurological diseases. Most recently, in December 2017 we entered into a collaboration with Biogen to identify new antisense drugs for the treatment of SMA. From inception through February 2018, we have generated over $810 million from our Biogen 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. In December 2016, the FDA approved SPINRAZA for the treatment of SMA in pediatric and adult patients. In January 2018, Biogen reported that SPINRAZA was available in over 30 markets. Through December 2017, we have earned $113.4 million in commercial revenue from SPINRAZA royalties. In addition to SPINRAZA royalties, from inception through February 2018, we have generated over $435 million in payments for SPINRAZA, including $90 million of milestone payments for the approval of SPINRAZA in the EU and Japan during 2017. We are receiving tiered royalties up to the mid-teens on any sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We paid Cold Spring Harbor Laboratory and the University of Massachusetts nominal amounts for license fees and milestone payments we received in 2017. We also pay a low single digit royalty on sales of SPINRAZA. Additionally, we owe a low single digit royalty on future sales of SPINRAZA. Biogen is responsible for all further global development, regulatory and commercialization activities and costs for SPINRAZA.

New antisense drugs for the treatment of SMA

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

Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense drugs to up to three targets to treat neurodegenerative diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. We are currently advancing IONIS-MAPT$_{Rx}$ (formerly IONIS-BIIB4$_{Rx}$) for AD under this collaboration. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization activities and costs for that drug. 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 an additional $210 million in a license fee and milestone payments per program, plus a mark-up of 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 sales from any drugs resulting from each of the three programs. From inception through February 2018, we have generated over $55 million in payments under this collaboration, including $10 million we received in 2017 for initiating a Phase 1/2a study of IONIS-MAPT$_{Rx}$.

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 drugs resulting from this collaboration. The exclusivity for neurological diseases will last through September 2019, and may be extended for any drug development programs Biogen is pursuing under the collaboration. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen will have the option to license antisense drugs 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 for a drug, it will assume all further global development, regulatory and commercialization responsibilities and costs for that drug. We are currently advancing five drugs, IONIS-SOD1$_{Rx}$ for ALS, IONIS-C9$_{Rx}$ (formerly IONIS-BIIB5$_{Rx}$), IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ under this collaboration. Biogen will be responsible for all of the drug discovery and development activities for drugs using other modalities.

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 drugs developed through 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. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any antisense drugs developed under this collaboration. If other modalities are chosen, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in milestone payments. In addition, we are eligible to receive tiered single-digit royalties on sales from any drugs using non-antisense modalities developed under this collaboration. From inception through February 2018, we have generated nearly $170 million in payments under this collaboration, including $15 million in milestone payments we received in 2017 for validating two undisclosed neurological disease targets.

For additional details about our collaboration agreements with Biogen, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Research, Development and Commercialization Partners

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 $75 million payment from Bayer. We are conducting a Phase 2b study evaluating IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, we plan to develop IONIS-FXI-L$_{Rx}$ through Phase 1. Following these studies and Bayer's decision to further advance these programs, Bayer will be responsible for all global development, regulatory and commercialization activities and costs for both drugs. We are eligible to receive additional milestone payments as each drug advances toward the market. In total over the term of our collaboration, we are eligible to receive up to $385 million in license fees, milestone 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 drugs combined. From inception through February 2018, we have generated over $175 million under this collaboration.

For additional details about our collaboration agreement with Bayer, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. In August 2017, as part of a reprioritization of its pipeline and strategic review of its Rare Diseases business, GSK declined its options for inotersen, our Phase 3 drug to treat people with ATTR, and IONIS-FB-L$_{Rx}$ (formerly IONIS-GSK4-L$_{Rx}$), an antisense drug to treat complement-mediated diseases. We are continuing to advance each of these drugs independently.

GSK, consistent with its focus on treatments for infectious diseases, continues to advance two drugs targeting hepatitis B virus, or HBV, under our collaboration: IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$. GSK is currently conducting Phase 2 studies for both of these drugs, which we designed to reduce the production of viral proteins associated with HBV infection. In March 2016, we and GSK amended the development plan for IONIS-HBV$_{Rx}$ to allow GSK to conduct all further development activities for this program. GSK has the exclusive option to license the drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee.

Under our agreement, if GSK successfully develops these drugs and achieves pre-agreed sales targets, we could receive license fees and milestone payments of more than $262 million. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance. From inception through February 2018, we have generated more than $162 million in payments under this alliance with GSK.

For additional details about our collaboration agreement with GSK, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Janssen Biotech, Inc.

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders of the GI tract. Janssen has the option to license drugs from us through the designation of a development candidate for up to three programs. Prior to option exercise we are responsible for the discovery activities to identify a development candidate. If Janssen exercises an option for one of the programs, it will be responsible for the global development, regulatory and commercial activities under that program. Under our collaboration, Janssen licensed IONIS-JBI1-2.5$_{Rx}$ in July 2016 and IONIS-JBI2-2.5$_{Rx}$ in November 2017. Under the terms of the agreement, we received $35 million in upfront payments. We are eligible to receive up to more than $800 million in milestone payments and license fees for these programs. In addition, we are eligible to receive tiered royalties up to the near teens on sales from any drugs resulting from this collaboration. From inception through February 2018, we generated more than $70 million in payments under this collaboration, including $10 million in 2017 for the license of IONIS-JBI2-2.5$_{Rx}$ and the initiation of a Phase 1 study of IONIS-JBI1-2.5$_{Rx}$.

For additional details about our collaboration agreement with Janssen, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Novartis

In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$. Under the collaboration agreement, Novartis has an exclusive option to develop and commercialize AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$. Akcea is responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the FDA and providing active pharmaceutical ingredient, or API, for each drug. If Novartis exercises an option for one of these drugs, Novartis will be responsible for all further global development, regulatory and commercialization activities and costs for such drug.

Akcea received a $75 million upfront payment in the first quarter of 2017, of which it retained $60 million and paid us $15 million as a sublicense fee. If Novartis exercises its option for a drug, Novartis will pay Akcea a license fee equal to $150 million for each drug it licenses. In addition, Akcea is eligible to receive up to $600 million and $530 million in milestone payments related to AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, respectively. Akcea plans to co-commercialize any licensed drug commercialized by Novartis in selected markets, under terms and conditions that it plans to negotiate with Novartis in the future, through the specialized sales force Akcea is building to commercialize volanesorsen. Akcea is also eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Akcea will pay 50 percent of these license fees, milestone payments and royalties to us as a sublicense fee.

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

For additional details about our and Akcea's collaboration agreement with Novartis, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Roche

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 IONIS-HTT_{Rx}, an antisense drug targeting HTT protein, through completion of our Phase 1/2a clinical study in people with early stage HD. In December 2017, upon completion of the Phase 1/2a study, Roche exercised its option to license IONIS-HTT_{Rx} and is now responsible for the global development, regulatory and commercialization activities for IONIS-HTT_{Rx}. 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. In addition, we are eligible to receive up to $137 million in milestone payments for each additional drug successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on sales from any product resulting from this alliance. From inception through February 2018, we have generated over $105 million in payments under this alliance with Roche, including $48 million in 2017 primarily for the license of IONIS-HTT_{Rx}.

For additional details about our collaboration agreement with Roche, including other financial information and termination provisions, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Satellite Company Partnerships

Achaogen, Inc.

In 2006, we exclusively licensed to Achaogen, Inc. specific know-how, patents and patent applications relating to aminoglycosides. In connection with the license, Achaogen issued to us $1.5 million of Achaogen stock. Achaogen is developing plazomicin, an aminoglycoside Achaogen discovered based on the technology we licensed to Achaogen. If Achaogen successfully develops and commercializes two drugs under our agreement, we will receive payments totaling up to $49.3 million for the achievement of key clinical, regulatory and sales events. The FDA set a PDUFA date of June 25, 2018 for plazomicin. Achaogen also plans to submit an MAA to the EMA in 2018. Through February 2018, we have generated $7 million in milestone payments from Achaogen. We are also eligible to receive low single digit royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development, regulatory and commercialization activities of plazomicin.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into an alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, 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 $5 million technology access fee, participation in fees from Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in milestone payments. We also have the potential to earn a portion of payments that Alnylam receives from licenses of our technology it grants to its partners, plus royalties. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded antisense therapeutics, ssRNAi therapeutics, and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam up to $3.4 million in milestone payments for specified development and regulatory events, plus royalties. To date, we do not have an RNAi-based drug in development.

In 2015, we and Alnylam entered into an alliance in which we formed an intellectual property cross-license under which 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. Through February 2018, we have generated over $73 million from Alnylam.

Antisense Therapeutics Limited

In 2001, we licensed ATL1102 and ATL1103 to ATL, an Australian company publicly traded on the Australian Stock Exchange. ATL completed a Phase 2a efficacy and safety trial and has also completed a chronic toxicology study in primates to support a potential Phase 2b trial of ATL1102 in people with MS. In addition, ATL is currently developing ATL1103 for growth and sight disorders. We are eligible to receive royalties on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103.

Atlantic Pharmaceuticals Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based specialty pharmaceutical company founded in 2006. Atlantic Pharmaceuticals is developing alicaforsen for the treatment of UC and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In 2017, under a rolling submission agreement with the FDA, Atlantic Pharmaceuticals filed the nonclinical data package of its NDA for alicaforsen to treat pouchitis. Alicaforsen has also been granted FDA Fast-Track designation, plus U.S. and European Orphan Drug designations for this indication. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. In 2010, Atlantic Pharmaceuticals began supplying alicaforsen under international named patient supply regulations for people with IBD for which we receive royalties. Under the agreement, we could receive milestone payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications.

Dynacure, SAS

In October 2016, we entered into a collaboration with Dynacure to discover, develop and commercialize an antisense drug for the treatment of neuromuscular diseases. We and Dynacure shared research responsibilities to identify a drug candidate. In November 2017, Dynacure licensed IONIS-DNM2-2.5_{Rx}, a drug targeting dynamin 2 for the treatment of centronuclear myopathy, from us. Upon licensing, Dynacure assumed all responsibility for development and commercialization for IONIS-DMN2-2.5_{Rx}. Under the terms of the agreement, we obtained a 15 percent equity ownership in Dynacure upon the initiation of the collaboration. We received additional equity and convertible notes in Dynacure for the license of IONIS-DMN2-2.5_{Rx} in 2017. We recorded a full valuation allowance for all of the equity and convertible debt we received from Dynacure because realization of value from the equity is uncertain. If Dynacure advances a target under this collaboration, we could receive cash or equity up to more than $210 million in a license fee and milestone payments for specified development, regulatory and sales events. In addition, we are eligible to receive royalties on future product sales of the drug under this collaboration.

Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-targeting therapeutics. We and Alnylam retain rights to develop and commercialize, on pre-negotiated terms, microRNA therapeutic products that Regulus decides not to develop either by itself or with a partner. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators of the genome, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development. MicroRNAs may also prove to be an attractive new tool for characterizing diseases. Regulus' focus is on drug discovery and development efforts for diseases with significant unmet medical need in organs to which we have been able to preferentially deliver oligonucleotide therapeutics effectively, such as the liver and kidney. Regulus currently has two drugs in clinical development. Regulus is studying RGLS4326 in a Phase 1 single ascending dose study designed to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of RGLS4326 administered subcutaneously in healthy volunteers. We are eligible to receive royalties on any future product sales of these drugs.

Suzhou Ribo Life Science Co., Ltd.

In April 2017, we entered into a collaboration with Ribo to develop and commercialize RNA-targeted therapeutics in China. We licensed IONIS-AR-2.5_{Rx}, IONIS-GCGR$_{Rx}$ and IONIS-EZH2-2.5_{Rx} to Ribo under our collaboration to develop and commercialize these drugs in China. In addition, Ribo will be responsible for conducting a multi-year research and drug discovery program to identify drugs that utilize our ssRNAi technology. Following the identification of a development candidate, Ribo may exercise its option to license each drug by paying us a license fee. For each drug that Ribo licenses, Ribo will be responsible for all development and commercialization activities and costs in China. We retained the rights to develop and commercialize ssRNAi technology and all drugs under the collaboration outside of China. Ribo will provide us a royalty-free license to the data and intellectual property created under the collaboration.

Under the agreement, we received an up-front payment of $2 million. We also obtained a nine percent equity ownership in Ribo. We are eligible to receive up to $153 million in license fees and milestone payments. In addition, we are eligible to receive tiered royalties up to the mid-twenty percent range on sales from any drugs resulting from this collaboration. From inception through February 2018, we have generated $2 million in payments under this collaboration with Ribo.

The University of Texas MD Anderson Cancer Center

In May 2016, we entered into a collaboration agreement with the University of Texas MD Anderson Cancer Center to identify cancer targets and create novel antisense drugs to treat cancer together. In the collaboration, we and MD Anderson are working together to validate novel "undruggable" cancer targets selected based on human genomic data. We are leading the drug discovery efforts against mutually agreed upon novel targets and MD Anderson is leading development activities through clinical proof of concept. Following clinical proof of concept, we and MD Anderson plan to identify a partner to complete development and to commercialize each drug with us leading business development efforts. Under the five year collaboration, we and MD Anderson will evenly share costs specific to our collaboration.

For additional details about our satellite company arrangements, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

External Project Funding

We are pursuing discovery and development projects that provide us with new therapeutic applications for antisense drugs. These programs represent opportunities for us and our technology. In some cases, we have funded these studies through support from our partners or disease advocacy groups and foundations.

CHDI Foundation, Inc.

Starting in November 2007, CHDI provided financial and scientific support to our Huntington's disease drug discovery program through our development collaboration. In April 2013, we formed an alliance with Roche to develop treatments for Huntington's disease. Under the terms of our agreement with CHDI, we will reimburse CHDI for a portion of its support of our Huntington's disease program out of the payments we receive from Roche.

Cystic Fibrosis Foundation

In August 2016, we entered into a collaboration agreement with the Cystic Fibrosis Foundation to discover and advance a drug for the treatment of Cystic Fibrosis. Under this agreement, we received upfront payments of $1 million and we are eligible to receive additional milestone payments of up to $2 million. Under the agreement, we and the Cystic Fibrosis Foundation will evenly share the first $3 million of costs specific to our collaboration. We are obligated to pay the Cystic Fibrosis Foundation up to $18 million upon achieving specific regulatory and sales events if we advance a drug under our collaboration. From inception through February 2018, we generated nearly $3 million under this collaboration, including $1 million we earned in 2017 for advancing IONIS-ENAC-2.5$_{Rx}$.

The Ludwig Institute; Center for Neurological Studies

In October 2005, we entered into a collaboration agreement with the Ludwig Institute, the Center for Neurological Studies and researchers from these institutions to discover and develop antisense drugs for ALS and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and Center for Neurological Studies modest milestone payments and royalties on any antisense drugs resulting from the collaboration.

For additional details about our external project funding collaborations, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Intellectual Property Sale and Licensing Agreements

We have a broad patent portfolio covering our products and technologies. We believe our patent estate represents the largest and most valuable nucleic acid therapeutics-oriented patent estate in the pharmaceutical industry. While the principal purpose of our intellectual property portfolio is to protect our products and those of our partners described above, our intellectual property is a strategic asset that we are exploiting to generate near-term revenues and that we expect will also provide us with revenue in the future. We have an active intellectual property sales and licensing program in which we sell or license aspects of our intellectual property to companies. Through this program, we also license our non-antisense patents. To date, we have generated more than $510 million from our intellectual property sale and licensing program that helps support our internal drug discovery and development programs.

In-Licensing Arrangements

University of Massachusetts

We have a license agreement with the University of Massachusetts under which we acquired an exclusive license to the University of Massachusetts' patent rights related to SPINRAZA. We paid the University of Massachusetts nominal amounts for license fees and milestone payments we received. We also pay a low single digit royalty on sales of SPINRAZA.

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to SPINRAZA. We paid Cold Spring Harbor Laboratory nominal amounts for license fees and milestone payments we received in 2017 and a low single digit royalty on sales of SPINRAZA. Additionally, we owe a low single digit royalty on future sales of SPINRAZA.

For additional details about our Intellectual Property Sale and Licensing arrangements, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Manufacturing

In the past, except for small quantities, it was generally expensive and difficult to produce chemically modified oligonucleotides like the antisense drugs we use in our research and development programs. As a result, 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 drugs, we found that the same techniques we used to efficiently manufacture one oligonucleotide drug could help improve the manufacturing processes for many other oligonucleotide drugs. By developing several proprietary chemical processes to scale up our manufacturing capabilities, we have greatly reduced the cost of producing oligonucleotide drugs. For example, we have significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing our capacity to make the drugs. Through both our internal research and development programs and collaborations with outside vendors we may achieve even greater efficiency and further cost reductions.

Our drug substance manufacturing facility is located in a 28,700 square foot building in Carlsbad, California. We purchased this building in 2017. In addition, we have a 25,800 square foot building that houses support functions for our manufacturing activities. We lease this facility under a lease that has an initial term ending in June 2021 with an option to extend the lease for up to two additional five-year periods. Our manufacturing facility is subject to periodic inspections by the FDA 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. We believe that with reasonably anticipated benefits from increases in scale and improvements in chemistry, we can manufacture antisense drugs at commercially competitive prices.

We believe we have sufficient manufacturing capacity to meet our current internal research, development and potential commercial needs, including the ongoing Phase 3 clinical trial we have for volanesorsen, as well as our current and future obligations under existing agreements with our partners for research, development and commercial needs. Specifically, we have the following in place for our approved drug, SPINRAZA and our drugs currently under regulatory review, volanesorsen and inotersen:

SPINRAZA

Pursuant to our collaboration with Biogen, Biogen is responsible for SPINRAZA drug supply. Biogen has contracted with us to manufacture API for SPINRAZA through September 2018.

Volanesorsen

We have supplied Akcea either through our manufacturing processes or through our outside vendors, including API and finished drug product to complete its ongoing clinical study for volanesorsen. We have also supplied the API and the finished drug product for volanesorsen's launch. We believe the API and drug product is adequate for at least the first two years of volanesorsen's launch. Akcea plans to leverage our relationships with contract manufacturing organizations, or CMO's, to procure its own long-term raw material and drug supplies at competitive prices in the future.

Inotersen

For inotersen's commercial launch, we are using CMOs to produce custom raw materials, API and finished goods. 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. Additionally, we continue to evaluate further relationships with additional suppliers to increase overall capacity as well as reduce further risks. While we believe that there are alternate sources of supply that can satisfy our commercial requirements, we cannot be certain that identifying and establishing relationships with such sources, if necessary, would not result in significant delay or material additional costs. We also cannot provide assurance that we will not 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.

We have manufactured limited supplies of our LICA drugs for our preclinical and clinical studies. We have purchased additional supplies of our LICA drugs through a CMO. LICA enables lower doses than unconjugated oligonucleotides. With our expertise in optimizing manufacturing of oligonucleotides, we believe we can develop new processes to scale up manufacturing of our LICA drugs at commercially competitive prices.

Patents and Proprietary Rights

Our success depends, in part, on our ability to obtain patent protection for our products in the United States 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 drug designs utilizing these chemically modified nucleosides. These core claims are each 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 drugs. 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, which applies to most of our drugs, and by creating multiple layers of patent protection for each of our specific drugs in development.

Type of Patent Claim		Description
1. Chemically Modified Nucleosides and Oligonucleotides	**Breadth** Broadly Applicable	1. Target and sequence independent
2. Antisense Drug Design Motifs		2. Sequence independent
3. Therapeutic Methods		3. Chemistry independent
4. Antisense Sequence		4. Specific claim to drug candidates
5. Drug Composition	Specific	

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 drugs to increase their therapeutic efficacy. Nucleosides and chemically modified nucleosides are the basic building blocks of our antisense drugs, therefore claims that cover any oligonucleotide incorporating one of our proprietary modified nucleosides can apply to a wide array of antisense mechanisms of action as well as several therapeutic targets. Of particular note are our patents covering our proprietary 2'-O-(2-methoxy) ethyl, or "MOE," modified nucleosides, incorporated into many of our second generation development compounds, as well as our constrained-ethyl nucleosides, or "cEt" nucleosides incorporated into our Generation 2.5 compounds.

The following are some of our patents in this category in key jurisdictions (U.S., Europe and Japan):

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	7,101,993	OLIGONUCLEOTIDES CONTAINING 2'O-MODIFIED PURINES	2023	Covers certain MOE nucleosides and oligonucleotides containing these nucleotides.
United States	7,399,845	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
United States	7,741,457	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
United States	8,022,193	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers oligonucleotides containing cEt nucleoside analogs.
United States	7,569,686	COMPOUNDS AND METHODS FOR SYNTHESIS OF BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers methods of synthesizing our cEt nucleosides.
Europe	EP1984381	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.
Europe	EP2314594	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt oligonucleotides and methods of use.
Japan	JP5342881	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Covers our cEt nucleosides and oligonucleotides containing these nucleoside analogs.

Antisense Drug Design Motifs

Other of our patents 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, or 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 drugs, including volanesorsen and inotersen, 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 drugs until March of 2023.

In addition, we have pursued patent claims to antisense drug design motifs incorporating bicyclic nucleoside analogs, which include both locked nucleic acids, or "LNA" and cEt. In Europe, we have been granted claims drawn to certain short gapmer oligonucleotides with bicyclic nucleosides, which include locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders. We have also successfully obtained issued patent claims covering our Generation 2.5 gapmer antisense drug design motifs that incorporate our cEt modified nucleosides. Santaris opposed granted European patents EP2092065 and EP2410053. In April 2015, the claims of EP2092065 were successfully upheld in amended form and in January 2017, EP2410053 was upheld with only minor amendment. The following patents are some examples of our issued patents in this category in key jurisdictions:

Jurisdiction	Patent/ Application No.	Title	Expiration	Description of Claims
United States	7,015,315	GAPPED OLIGONUCLEOTIDES	2023	2'-O-alkyl-O-alkyl gapmer oligonucleotides.
Europe	EP2021472	COMPOUNDS AND METHODS FOR MODULATING GENE EXPRESSION	2027	Short gapmer oligonucleotides, having wings of 2 bicyclic nucleosides, and a gap of 10 deoxynucleotides for the treatment of cardiovascular or metabolic disorders
United States	7,750,131	5'-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	5'-Methy BNA containing gapmer compounds
Europe	EP2092065	ANTISENSE COMPOUNDS	2027	Gapmer compounds having wings comprised of 2'-modifed and LNA nucleosides
Europe	EP2410053	ANTISENSE COMPOUNDS	2027	Gapmer compounds having wings comprised of 2'-MOE and bicyclic nucleosides
Japan	JP 5665317	ANTISENSE COMPOUNDS	2027	Gapmer compounds having wings comprised of 2'-MOE and bicyclic nucleosides
Europe	EP2673361	OLIGOMERIC COMPOUNDS COMPRISING BICYCLIC NUCLEOTIDES AND USES THEREOF	2032	Gapmer having at least one bicyclic nucleoside, 2'-modified nucleoside, and 2'-deoxynucleoside in either the 5'- or 3'-wing.

LIgand-Conjugated Antisense (LICA) Technology

We have also pursued patent claims to new chemistries created to enhance targeting of antisense drugs to specific tissues and cells in order to improve a drug's properties. Our N-acetyl-galactosamine, or GalNAc, LICA drugs are designed 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/ Application No.	Title	Expiration	Description of Claims
United States	9,127,276	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE	2034	Covers our primary 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	Covers our primary 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

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 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.

Survival Motor Neuron and SPINRAZA

SPINRAZA is protected from generic competition in the United States until at least 2030 and in Europe until 2026 by a suite of patents. These issued patents include: (i) the Bennett patent related to methods of altering mRNA processing (e.g., splicing, the mechanism of action of SPINRAZA) with a fully modified 2'MOE oligonucleotide, (ii) a patent 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 (iii) 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. Those patents protect SPINRAZA from generic and antisense innovator competition in the United States until at least 2030. 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 the key U.S. and European issued patents protecting SPINRAZA:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	6,210,892	ALTERATION OF CELLULAR BEHAVIOR BY MODULATION OF MRNA PROCESSING	2018	Altering mRNA processing with a fully modified 2'MOE oligonucleotide.
United States	8,361,977	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2030	Sequence and chemistry (full 2'-MOE) of SPINRAZA
Europe	1910395	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2026	Sequence and chemistry (full 2'-MOE) of SPINRAZA
United States	7,838,657	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2027	Oligonucleotides having sequence of SPINRAZA (chemistry independent)
United States	8,110,560	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2025	Methods of using antisense oligonucleotides having sequence of SPINRAZA to alter splicing of SMN2 and/or to treat SMA
United States	8,980,853	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2030	Methods of administering SPINRAZA

Apolipoprotein C-III and volanesorsen

We have obtained patent claims in the United States drawn to the use of antisense compounds complementary to a broad active region of human Apo C-III, including the site targeted by volanesorsen. We have secured similar claims to compounds complementary to any site on human Apo C-III in Australia. We have also obtained issued patent claims to the specific antisense sequence and chemical composition of volanesorsen in the United States, Australia, Canada, Hong Kong and Europe. The issued U.S. claims protect volanesorsen from generic competition in the United States until at least 2023. In addition, upon approval of volanesorsen by the FDA, we will seek patent term extension to recapture a portion of the term lost during FDA regulatory review, extending the term of this patent beyond 2023. We are pursuing additional patent applications designed to protect volanesorsen worldwide. The table below lists the issued patents in key jurisdictions:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	9,624,496	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Antisense compound specifically hybridizable within the nucleotide region of apoCIII targeted by volanesorsen
United States	7,598,227	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Methods of treating hyperlipidemia, lowering cholesterol levels or lowering triglyceride levels with volanesorsen
United States	7,750,141	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Antisense sequence and chemistry of volanesorsen
Europe	EP1622597	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2024	Antisense sequence and chemistry of volanesorsen
Europe	EP2441449	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2024	Antisense compound specifically hybridizable within the nucleotide region of apoCIII targeted by volanesorsen
United States	9,157,082	MODULATION OF APOLIPOPROTEIN CIII (APOCIII) EXPRESSION	2032	Methods of using APOCIII antisense oligonucleotides for reducing pancreatitis and chylomicronemia and increasing HDL
Japan	JP 6203707	MODULATION OF APOLIPOPROTEIN CIII (APOCIII) EXPRESSION	2032	Methods of using APOCIII antisense oligonucleotides having the sequence of volanesorsen for treating pancreatitis
United States	9,593,333	MODULATION OF APOLIPOPROTEIN C-III (APOCIII) EXPRESSION IN LIPOPROTEIN LIPASE DEFICIENT (LPLD) POPULATIONS	2034	Methods of using APOCIII specific inhibitors for treating lipoprotein lipase deficiency

Transthyretin and inotersen

We obtained issued claims covering inotersen in the United States. The issued U.S. claims protect inotersen from generic competition in the United States until at least 2031. We are also pursuing additional patent applications designed to protect inotersen in foreign jurisdictions. The table below lists the current issued patents protecting inotersen in key jurisdictions:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	8,101,743	MODULATION OF TRANSTHYRETIN EXPRESSION	2025	Antisense sequence and chemistry of inotersen
United States	8,697,860	DIAGNOSIS AND TREATMENT OF DISEASE	2031	Composition of inotersen
United States	9,061,044	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Sodium salt composition of inotersen
United States	9,399,774	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Methods of treating transthyretin amyloidosis by administering inotersen
Japan	JP5896175	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Composition of inotersen
Europe	EP2563920	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Composition of inotersen

We seek patent protection in significant markets and/or countries for each drug 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 drug will prevent generic drugs 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 United States 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 United States and foreign governmental authorities governs the development, manufacture and sale of our drugs. In particular, our drugs are subject to a number of approval requirements by the FDA in the United States 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 drugs. 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 drug 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 unapproved drug before a manufacturer can market it in the United States. 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 drug, it will issue an approval letter authorizing commercial marketing of the drug and may require a risk evaluation and mitigation strategy, or REMS, to help ensure the benefits of the drug outweigh the potential risks. The requirements for REMS can materially affect the potential market and profitability of our drugs. In foreign jurisdictions, the drug approval process is similarly demanding.

Numerous regulatory authorities in addition to the FDA, including, in the United States, the Centers for Medicare & Medicaid Services, other divisions of the U.S. Department of Health and Human Services, the U.S. Department of Justice, and similar foreign, state and local government authorities, regulate sales, promotion and other activities following drug approval. Only those claims relating to safety and efficacy that the FDA has approved may be used in labeling. Promotional communications regarding a drug must be consistent with the information in the drug's approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses.

For any approved drug, domestic and foreign sales of the drug depend, in part, on the availability and amount of reimbursement by third party payors, including governments and private health plans. Private health plans may seek to manage cost and use of our drugs by implementing coverage and reimbursement limitations. Governments may also regulate or influence coverage, reimbursement and/or pricing of our drugs to control cost or affect use. Within the EU a variety of payors pay for drugs, 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, including Akcea, to successfully commercialize approved drugs.

In the United States 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 United States 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 drugs.

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.

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

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

Competition

Our Business in General

Some of our drugs may compete with existing therapies for market share. 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 specialized pharmaceutical firms and large pharmaceutical companies acting either independently or together with biopharmaceutical companies. Our drugs are differentiated from traditional small molecule drugs 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 drugs target for which we have or may receive marketing authorization will determine our competition. For some of our products, an important factor in competition 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 among 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.

The current key competition for SPINRAZA, our marketed drug for the treatment of people with SMA, and volanesorsen and inotersen, our drugs currently under regulatory review for the treatment of people with FCS and hATTR, respectively, is set forth below.

SPINRAZA

We believe that the following drugs could compete with SPINRAZA:

Drug	Company	Drug Description	Phase	Admin/Dosing	Efficacy(1)	Safety(1)
AVXS-101	AveXis	Gene therapy that corrects the SMN1 gene using the AAV9 Vector	Pivotal	Infusion	As of January 20, 2017, in the Phase 1 OLE, the 12 patients taking the proposed therapeutic dose of AVXS-101 were event free and were a median age of 20.2 months at their last follow up appointment. Additionally, 10 out of the 12 patients achieved the ability to sit unassisted for at least 5 seconds, including one patient whose achievement of this milestone was confirmed after January 20, 2017.	Generally well tolerated to date, no new treatment-related SAEs or AEs observed
RG7916	PTC Therapeutics/ Roche/ SMA Foundation	A small molecule drug that modulates splicing of the SMN2 gene	2	Oral	None reported	Safe and well tolerated at all doses and had no drug-related or safety-related study withdrawals.
LMI070	Novartis	A small molecule drug that modulates splicing of the SMN2 gene	1/2	Oral	None reported	Study was placed on clinical hold in May 2016 due to safety findings reported in animal studies. The clinical hold was removed in September 2017 and dosing resumed along with additional monitoring.

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

We believe that SPINRAZA's closest competitor is AVXS-101. AVXS-101 is currently in a pivotal study for infants with Type 1 SMA using natural history as a comparator. Avexis initiated this study in September 2017 and plans to enroll 15 patients. AveXis has incorporated EU specific Scientific Advice from the EMA into its European pivotal study. While the data released thus far on the AVXS-101 study is encouraging, it is still early in development, having just initiated its first of two pivotal studies. In addition, other gene therapies have had difficulty providing lasting therapeutic benefit. Also AveXis has stated it needs to scale its manufacturing capabilities to be able to manufacture larger quantities of AVXS-101 GMP drug for their pivotal studies in Type 1, ongoing Phase 1 studies in Type 2 patients, and future studies in patients with Type 3 SMA. Further, no company has yet to successfully commercialize a gene replacement therapy, which may create significant barriers for AVXS-101.

Volanesorsen

We believe that the following drugs could compete with volanesorsen:

Drug	Company	Drug Description	Phase	Admin/Dosing	Efficacy(1)	Safety(1)
Metreleptin	Novelion Therapeutics	A synthetic form of the hormone leptin	3	Reconstituted subcutaneous injection	44.4% mean reduction in triglycerides at four months in patients with abnormal triglyceride levels	Anti-metreleptin antibodies, hypoglycemia, hypersensitivity, risk of T-cell lymphoma
Gemcabene	Gemphire Therapeutics	Monocalcium salt of a dialkyl ether dicarboxylic acid	2	Oral, once-daily	In a post hoc analysis (n=9) of patients with triglycerides >500 mg/dl, reductions of 59% and 60% from 150mg and 300mg doses, respectively, were observed	In a recent study, in the gemcabene-treatment group, the most frequently occurring adverse events were headache and infection

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

Metreleptin is being tested in people with FPL who also have NASH. In December 2016, Novelion submitted a marketing authorization application to the EMA seeking approval for Metreleptin as replacement therapy to treat complications of leptin deficiency in a small subset of people with FPL and in people with generalized lipodystrophy, or GL. An investigator-sponsored study is currently ongoing with the support of Novelion to evaluate Metreleptin in people with FPL who also have NASH. Metreleptin does not affect apoC-III levels. ApoC-III levels have been shown to be elevated in people with FPL, and directly correlate to triglyceride levels.

Gemcabene is being studied in people with severe hypertriglyceridemia, defined as triglycerides above 500 mg/dL and Gemphire expects to report top-line results from its Phase 2 study in the second quarter of 2018.

Volanesorsen for the treatment of FCS is currently under regulatory review for marketing authorization in the U.S., EU and Canada. To date, volanesorsen has shown the highest percent of triglyceride reductions compared to existing treatments, such as fibrates, regardless of starting triglyceride levels prior to dosing with volanesorsen. Based on our broad Phase 2 data for the treatment of different patients including people with FCS, we believe that volanesorsen will work equally well as a single agent or in combination with other triglyceride-lowering drugs on the market. If regulatory authorities require us to implement platelet monitoring procedures in the commercial setting, which have yet to be determined, it could impact the future competitive profile of volanesorsen.

Inotersen

We believe that the following drugs could compete with inotersen:

Drug	Company	Drug Description	Phase	Admin/Dosing	Efficacy(1)	Safety(1)
Patisiran	Alnylam	An RNAi drug formulated with lipid nanoparticles to inhibit TTR mRNA	Registration	Infusion every 3 weeks with pre-treatment with steroids	84.3% mean reduction in TTR at 18 months	Most common adverse events more frequently observed in patisiran arm vs. placebo were peripheral edema (29.7% vs. 22.1%) and infusion-related reactions (18.9% vs. 9.1%)
Tafamidis	Pfizer	A small molecule drug to stabilize TTR Protein	3 to support refiling in the U.S., Approved in the EU	Daily oral capsule	In 45% of people taking Tafamidis, nerve function either improved or stabilized, compared with 30% of patients taking placebo	Urinary tract infection, vaginal infection, upper abdominal pain and diarrhea
Diflunisal	N/A Generic	A non-steroid anti-inflammatory agent	Approved (but not for ATTR)	Daily oral capsule/doses	Improved nerve function as shown by lower Neuropathy Impairment Score plus 7 nerve tests, or NIS+7. The NIS+7 score increased by 25.0 points in the placebo group versus 8.7 points in the diflunisal group	In two studies repurposing diflunisal for use in TTR amyloidosis, drug-related adverse events that led to discontinuation were: gastrointestinal bleeding, low platelets, deterioration of renal function, congestive heart failure, glaucoma and nausea.
Tolcapone	SOM Biotech	Small molecule repurposed generic drug	2	Daily oral dose	Shows binding and stabilization of TTR in humans	No drug related adverse events reported
ALN-TTRsc02	Alnylam	An RNAi drug conjugated with GalNAC to inhibit TTR mRNA in liver cells	1	Monthly or quarterly	In healthy volunteers, a single dose showed mean max TTR knockdown of 97%	Injection site reactions were reported

(1) Taken from public documents including respective company press releases, company presentations, and scientific presentations. Diflunisal efficacy and safety came from the published papers of two investigator sponsored studies, Berk JL, Suhr OB, Obici L, et al. Repurposing Diflunisal for Familial Amyloid Polyneuropathy: A Randomized Clinical Trial. JAMA. 2013;310(24):2658-2667 and Sekijima YS, Toja K, Morita H, et al. Safety and efficacy of long-term diflunisal administration in hereditary transthyretin (ATTR) amyloidosis. Amyloid. 2015;22(2):79-83.

We believe that of the drugs that are in development or on the market, inotersen's closest competitor is patisiran. Alnylam is developing patisiran for hATTR. Patisiran is an intravenously administered RNAi molecule that is formulated with lipid nanoparticles to enable delivery of the drug to the liver. It is administered via an infusion by a healthcare provider in a clinical setting every three weeks. People receiving patisiran are pretreated with steroids to prevent infusion related reactions. In October 2016, Alnylam discontinued development of revusiran, its drug for the cardiomyopathy form of TTR amyloidosis, due to a safety finding in its Phase 3 study. Revusiran was a subcutaneously administered RNAi molecule that was Alnylam's first generation GalNAc drug and was dosed at 500 mg per week as two subcutaneous injections. Alnylam completed Phase 1 studies of its second generation GalNAC, ALN-TTRsc02. Because we have a PDUFA date of July 6, 2018 for inotersen and Alnylam's PDUFA date for patisiran is August 11, 2018, we believe that inotersen could be the first RNA-targeted drug on the market for the treatment of people with hATTR. We also believe that the overall product profile of inotersen, as a once weekly, subcutaneous injection with no pretreatment has advantages to the drugs detailed above, however potential platelet and renal monitoring requirements in the commercial setting, which have yet to be determined, could impact the future competitive profile of inotersen.

Employees

As of February 20, 2018, we employed 547 people, including 100 Akcea employees. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees, and management considers relations with our employees to be good.

Executive Officers of Ionis

The following sets forth certain information regarding our executive officers as of February 20, 2018:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	72	Chairman, Chief Executive Officer and President
Brett P. Monia, Ph.D.	56	Chief Operating Officer and Senior Vice President, Drug Discovery and Corporate Development
C. Frank Bennett, Ph.D.	61	Senior Vice President, Antisense Research
Sarah Boyce	46	Chief Business Officer
Richard S. Geary, Ph.D.	60	Senior Vice President, Development
Elizabeth L. Hougen	56	Senior Vice President, Finance and Chief Financial Officer
Patrick R. O'Neil, Esq.	44	Senior Vice President, Legal, General Counsel, Chief Compliance Officer and Corporate Secretary

Management Transitions

In January 2018 Brett Monia, a founder of Ionis, and head of Drug Discovery, and the inotersen program, was promoted to Chief Operating Officer. In his new role, in addition to continuing to play a key role in drug discovery and development including taking responsibility for the research to development transition, Dr. Monia assumed responsibilities for the company's regulatory, patient advocacy, human resources and business functions including corporate communications, investor relations, business development, alliance management and competitive intelligence. B. Lynne Parshall, who has been with Ionis for 27 years, became Senior Strategic Advisor to Ionis and remains a member of the Board of Directors of Ionis and Akcea. In addition to supporting Dr. Monia in his transition, Ms. Parshall is continuing to be involved in strategic planning, business development, and with Ionis' important relationships with Biogen and Akcea.

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

Chairman, Chief Executive Officer and President

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

BRETT P. MONIA, Ph.D.

Chief Operating Officer and Senior Vice President, Drug Discovery and Corporate Development

Dr. Monia was promoted to Chief Operating Officer in January 2018 and to Senior Vice President, Drug Discovery and Corporate Development in January 2012. 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.

Senior Vice President, Antisense Research

Dr. Bennett was promoted to Senior Vice President, Antisense Research in January 2006. 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.

SARAH BOYCE

Chief Business Officer

Ms. Boyce joined Ionis in January 2015 as our Chief Business Officer. Prior to joining Ionis, Ms. Boyce was Vice President, Head of International Business Strategy and Operations at Forest Laboratories, Inc. from 2012 to 2014. She was Vice President, Global Head Nephrology Therapeutics Area of Alexion Pharmaceuticals from 2010 to 2011. She held various positions at Novartis Group AG, including Vice President, Global Program Head, Pediatric and Specialty from 2000 to 2010. Prior to that, Ms. Boyce held positions at Bayer Pharmaceuticals and Roche.

RICHARD S. GEARY, Ph.D.

Senior Vice President, Development

Dr. Geary was promoted to Senior Vice President, Development in August 2008. From August 2003 to August 2008, Dr. Geary served as our Vice President, Preclinical Development. From November 1995 to August 2003, he held various positions within the Preclinical Development department. Prior to joining Ionis in 1995, Dr. Geary was Senior Research Scientist and Group Leader for the bioanalytical and preclinical pharmacokinetics group in the Applied Chemistry Department at Southwest Research Institute.

ELIZABETH L. HOUGEN

Senior Vice President, Finance and Chief Financial Officer

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

PATRICK R. O'NEIL, Esq.

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

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

Item 1A. RISK FACTORS

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

Risks Associated with our Ionis Core and Akcea Therapeutics Businesses

If the market does not accept our drugs, including SPINRAZA, volanesorsen and inotersen, we are not likely to generate revenues or become consistently profitable.

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

Additionally, in many of the markets where we may sell our drugs in the future, if we cannot agree with the government regarding the price we can charge for our drugs, then we may not be able to sell our drugs in that market. Similarly, cost control initiatives by governments or third party payors could decrease the price received for our drugs or increase patient coinsurance to a level that makes our drugs, including SPINRAZA, volanesorsen and inotersen, unaffordable.

The degree of market acceptance for our drugs, including SPINRAZA, volanesorsen and inotersen, 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 drugs and their potential advantages over competing products;
- cost and effectiveness of our drugs compared to other available therapies;
- patient convenience of the dosing regimen for our drugs; and
- reimbursement policies of government and third-party payors.

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any drugs that we may develop. For example, in the clinical studies with volanesorsen and inotersen, declines in platelet counts were observed in many patients and some patients discontinued the studies because of platelet declines. In addition, in the inotersen NEURO-TTR study, safety signals related to renal function were observed. Therefore, we expect the product label for volanesorsen and inotersen will require periodic platelet monitoring and the product label for inotersen will require periodic renal monitoring, which could negatively affect our ability to attract and retain patients for these drugs. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help manage these safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. While we believe we and Akcea can better maintain patients on inotersen and volanesorsen through patient-centric commercial approachs where we and Akcea plan to have greater involvement with physicians and patients, if we and Akcea cannot effectively maintain patients on inotersen or volanesorsen, we may not be able to generate substantial revenue from inotersen or volanesorsen sales.

If we or our partners fail to compete effectively, our drugs, including SPINRAZA, volanesorsen and inotersen, will not contribute significant revenues.

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

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

These competitive developments could make our drugs, including SPINRAZA, volanesorsen and inotersen, obsolete or non-competitive.

Certain of our partners are pursuing other technologies or developing other drugs 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 drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs, including SPINRAZA, volanesorsen and inotersen.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies of new pharmaceutical products in obtaining FDA and other regulatory authorizations of such products and in commercializing such products. Accordingly, our competitors may succeed in obtaining regulatory authorization for products earlier than we do. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and we will primarily rely on our partners, and Akcea to provide this capability.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of products in our development pipeline. For example, AVXS-101, RG7916, and LMI070 could compete with SPINRAZA and metreleptin and Gemcabene could compete with volanesorsen; patisiran, tafamadis, diflunisal, tolcapone, PRX004 and ALN-TTRsc02 could compete with inotersen.

Following approval, our drugs, including SPINRAZA, volanesorsen and inotersen could be subject to regulatory limitations.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our drug products, including SPINRAZA, volanesorsen and inotersen.

The FDA and foreign regulatory authorities have the authority to impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities.

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. If the results of such post-marketing studies are not satisfactory, the FDA or a foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill.

If we or others identify side effects after any of our drug products are on the market, or if manufacturing problems occur subsequent to regulatory approval, we or our partners may lose regulatory approval, or we or our partners may need to conduct additional clinical studies and/or change the labeling of our drug products including SPINRAZA, volanesorsen and inotersen.

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

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

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

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

Our collaboration with Biogen may not continue for various reasons. Biogen can terminate our collaboration at any time. If Biogen stops developing or commercializing SPINRAZA, we would have to seek or spend additional funding and SPINRAZA's development and 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 effectively build and manage a distribution, medical affairs, market access, marketing and sales infrastructure for inotersen, or have a commercial partner perform these functions, it could delay, harm or preclude the commercial launch of inotersen and the related product revenue.

We plan to commercialize inotersen in North America ourselves and to seek a commercial partner in other geographic regions. We currently have a limited commercial infrastructure to distribute, market and sell inotersen. If approved, to commercialize inotersen, we must build these capabilities, have a commercial partner perform these functions, or make arrangements with third parties to perform these services. There are significant risks involved in building and managing a commercial infrastructure. We may not be successful in doing so.

We may contract with, and rely on, third party specialty pharmacies to distribute inotersen. A specialty pharmacy is a pharmacy that specializes in dispensing medications for complex or chronic conditions, a process that requires a high level of patient education and ongoing management. Absent a commercial partner, our management team will need to devote a significant amount of attention to building and managing this distribution network. The use of specialty pharmacies involves certain risks, including but not limited to risks that these organizations will not provide us with accurate or timely information, not effectively sell or support our drug products, not satisfy financial obligations to us, or cease operations.

We may also build a specialty sales force in each global region we expect to market inotersen, leverage the sales infrastructure of a commercial partner, or utilize a third-party marketing and sales organization. It will be expensive and time consuming for us to build and establish our own sales force and related compliance protocols to market inotersen. We will have to compete with other companies to recruit, hire, train, manage and retain sales personnel.

We will also incur expenses prior to product launch to develop our distribution, medical affairs, market access, marketing and sales infrastructure. If there is a delay in the commercial launch of inotersen, we will incur additional expenses for having developed these capabilities earlier than required and prior to realizing any revenue from sales of inotersen.

If we cannot effectively build and manage our distribution, medical affairs, market access, marketing and sales infrastructure, or find a suitable commercial partner to perform such functions, the commercial launch and sales of inotersen may be delayed, less successful or precluded. Such events may result in decreased sales and lower revenue, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

If government or other third-party payors fail to provide adequate coverage and payment rates for our drugs, including SPINRAZA, inotersen and volanesorsen, our revenue will be limited.

In both domestic and foreign markets, sales of our current and future products will depend in part upon the availability of coverage and reimbursement from third-party payors. The majority of people in the United States who would fit within our target patient populations for our drugs 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 drug products 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 drugs affordable.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. For example, in the United States, recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several U.S. Congressional inquiries and proposed federal legislation designed to, among other things, reform government program reimbursement methodologies for drug products and bring more transparency to drug pricing. Third-party coverage and reimbursement for our products or drugs may not be available or adequate in either the United States or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

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

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

If we or our partners fail to obtain regulatory approval for our drugs, including volanesorsen, inotersen, and additional approvals for SPINRAZA, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs, including volanesorsen and inotersen, will be considered safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that SPINRAZA will be approved in additional markets or for additional indications. We and our partners must conduct time-consuming, extensive and costly clinical studies to show the safety and efficacy of each of our drugs before they can be approved for sale. We 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 drugs. It is possible that regulatory agencies will not approve our drugs including, volanesorsen and inotersen for marketing or additional marketing authorizations for SPINRAZA. 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 drugs, including SPINRAZA, volanesorsen and inotersen, the agency will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the drug. For example, the FDA or foreign regulatory authorities could claim that we have not tested volanesorsen in a sufficient number of patients to demonstrate volanesorsen is safe and effective in patients with FCS or FPL to support an application for marketing authorization, especially since a small number of patients in the APPROACH FCS study experienced severe thrombocytopenia, a condition where the patient has severely low platelet levels. In such a case, we may need to conduct additional clinical studies before obtaining marketing authorization, which would be expensive and cause delays.

The FDA's Division of Metabolism and Endocrinology Products advisory committee is scheduled to discuss and advise the FDA on the risk-benefit profile of volanesorsen for the treatment of FCS on May 10, 2018. In advance of this advisory committee meeting, we, Akcea and the FDA will submit briefing documents for the committee's review, and these briefing documents will be made available to the public and may include information from the volanesorsen development program that have not previously been disclosed. Historically, for some companies, disclosure of information in this manner has led to increased volatility in their stock price. The advisory committee and FDA may interpret nonclinical and clinical data differently than we and our experts have. Press coverage and public scrutiny of the materials that will be discussed at the advisory committee meeting may negatively affect the potential for the NDA for volanesorsen to receive approval or the trading price of our securities. Even if we and Akcea ultimately obtain approval for volanesorsen, the matters discussed at the advisory committee meeting could limit Akcea's ability to successfully commercialize volanesorsen.

Failure to receive marketing authorization for our drugs, volanesorsen and inotersen, or additional authorizations for SPINRAZA, or delays in these authorizations could prevent or delay commercial introduction of the drug, 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 drugs 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 drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs are safe and effective for human use, we may need to abandon one or more of our drug development programs.

In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur in clinical studies for our drugs, including the study of volanesorsen in patients with FPL. If any of our drugs in clinical studies, including volanesorsen, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for the drug and our stock price could decline.

Even if our drugs are successful in preclinical and human clinical studies, the drugs 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 drugs in development, may not predict the results of subsequent clinical studies, including the Phase 3 study of volanesorsen in patients with FPL. 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 drug on subjects in the trial;
- we 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;
- 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;
- the cost of our clinical studies may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

In addition, our current drugs, including SPINRAZA, volanesorsen and inotersen, are chemically similar to each other. As a result, a safety observation we encounter with one of our drugs could have, or be perceived by a regulatory authority to have, an impact on a different drug 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 drugs 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 drugs: 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. Similarly, we have an ongoing Phase 3 study of volanesorsen in patients with FPL, an ongoing open label extension study of volanesorsen in patients with FCS, an ongoing open label extension study of inotersen and expanded access programs for each drug. Adverse events or results from these studies could negatively impact our current or planned marketing approval applications for volanesorsen in patients with FCS, for inotersen or the commercial opportunity for each product.

Any failure or delay in the clinical studies, including the Phase 3 study for volanesorsen in patients with FPL, could reduce the commercial potential or viability of our drugs.

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

To successfully commercialize any of our drugs, we or our partner would need to establish large-scale commercial manufacturing capabilities either on our own or through a third party manufacturer. We and Akcea will rely on third party manufacturers to supply the drug substance and drug product for inotersen and volanesorsen. 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 drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our drug costs. We may not be able to manufacture our drugs at a cost or in quantities necessary to make commercially successful products.

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

We depend on third parties to conduct our clinical studies for our drugs 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 drugs and expect to continue to do so in the future. For example, we use clinical research organizations, such as Icon Clinical Research Limited, INC Research Toronto, Inc. and Medpace for the clinical studies for our drugs, including volanesorsen and inotersen. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule, or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, marketing authorization and commercialization of our drugs, including authorizations for volanesorsen and inotersen or additional authorizations for SPINRAZA.

Risks Associated with our Businesses as a Whole

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of December 31, 2017, we had an accumulated deficit of approximately $1.2 billion and stockholders’ equity of approximately $418.7 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our income has come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. We may incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or achieve or sustain future profitability.

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

As described above, we have incurred net losses. 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.

As of December 31, 2017, we had federal and California net operating loss carryforwards of approximately $561.1 million and $887.1 million, respectively. The federal net operating loss carryforwards will begin to expire, if not utilized, beginning in 2024. These net operating loss carryforwards could expire unused and be unavailable to offset future income tax liabilities. Under the Tax Cut and Jobs Act of 2017, or the Tax Act, federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating losses is limited. It is uncertain if and to what extent various states will conform to the newly enacted federal tax law. In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, 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. It is possible that we have experienced an ownership change limitation. 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 is materially limited, it would harm our future operating results by effectively increasing our future tax obligations.

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

To date, corporate partnering has played a significant role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our unpartnered drugs. 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 drugs could suffer.

Our corporate partners are developing and/or funding many of the drugs in our development pipeline. If any of these pharmaceutical companies stops developing and/or funding these drugs, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these drugs 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 on inotersen 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 drugs.

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, Novartis and Roche these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we first anticipated.

For example, a collaborator such as AstraZeneca, Bayer, Biogen, GSK, Novartis 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 drug 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 drugs than it does for its own drugs.

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 drugs, including SPINRAZA.

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 drug will enter the clinic, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, marketing authorization. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors' expectations, including milestones related to SPINRAZA, volanesorsen and inotersen the price of our securities could decrease.

If we cannot protect our patents 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 and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, other partners 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.

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 sometimes need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the United States Patent and Trademark Office or the International Trade Commission or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business. For example, in November 2013 we filed a patent infringement lawsuit against Gilead Sciences Inc. in the United States District Court of the Northern District of California. Intellectual property lawsuits may be costly and may not be resolved in our favor.

If a third party claims that our drugs 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 United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain.

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

Many of our drugs are undergoing clinical studies or are in the early stages of research and development. All of our drug programs will require significant additional research, development, preclinical and/or clinical testing, marketing authorization and/or commitment of significant additional resources prior to their successful commercialization. As of December 31, 2017, we had cash, cash equivalents and short-term investments equal to $1.0 billion. If we do not meet our goals to successfully commercialize our drugs, including SPINRAZA, volanesorsen and inotersen, or to license our drugs 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 for SPINRAZA;
- marketing approvals for volanesorsen and inotersen;
- the profile and launch timing of our drugs, including volanesorsen and inotersen;

- 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 drugs.

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.

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, 2017, the market price of our common stock ranged from $65.51 to $37.26 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, governmental regulation, marketing authorization, changes in payors' reimbursement policies, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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, volanesorsen and inotersen. 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, products liability claims may result in decreased demand for our drug products, 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.

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 affected. We manufacture the finished drug product for volanesorsen and inotersen at third party contract manufacturers.

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 drugs.

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. The facilities and the equipment we and our contract manufacturers use to research, develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Our facilities or our contract manufacturers may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism; and if our facilities are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, 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 and operations would suffer in the event of computer system failures.

Despite the implementation of security measures, our internal computer systems, and those of our clinical research organizations, manufacturers, commercial partners and other third parties on which we rely, are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If issues were to arise and cause interruptions in our operations, it could result in a material disruption of our drug programs. For example, the loss of clinical study data from completed or ongoing clinical studies could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development or commercialization of our drugs, including SPINRAZA, volanesorsen and inotersen could be harmed or delayed.

Provisions in our certificate of incorporation, other agreements 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.

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 10.3 million shares of our common stock upon conversion of our convertible senior notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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.

The recently passed comprehensive tax reform bill could adversely affect our business and financial condition.

The Tax Act significantly revises the Internal Revenue Code of 1986, as amended. The Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35 percent to a flat rate of 21 percent, limitation of the tax deduction for interest expense to 30 percent of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80 percent of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain if and to what extent various states will conform to the newly enacted federal tax law. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. We urge our stockholders to consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common stock.

We could be subject to additional tax liabilities.

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

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

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

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 20, 2018, we occupied the following properties:

Property Description	Location	Square Footage	Owned or Leased	Initial Lease Term End Date	Lease Extension Options
Ionis laboratory and office space facility	Carlsbad, CA	176,000	Owned		
Ionis manufacturing facility	Carlsbad, CA	28,700	Owned		
Ionis manufacturing support facility	Carlsbad, CA	25,800	Leased	2021	Two, five-year options to extend
Akcea office space facility	Cambridge, MA	6,100	Leased	2018	None
Akcea office space facility	Cambridge, MA	3,100	Leased	2020	None
		239,700			

We believe our existing facilities are adequate for our requirements in the foreseeable future and that we have sufficient manufacturing capacity to meet our current and future obligations under existing agreements with our partners for commercial, research and development needs and to produce launch quantities for volanesorsen and inotersen. Akcea will need additional space in the future as it continues to build its development, commercial and support teams. Akcea is currently searching for a new office facility and believes it can find suitable space on commercially reasonable terms.

Item 3. Legal Proceedings

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712, which are jointly owned by Merck Sharp & Dohme Corp. and Ionis Pharmaceuticals, Inc. In the suit Gilead asked the court to determine that Gilead's activities do not infringe any valid claim of the named patents and that the patents are not valid. We and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents infringes those patents, and requesting monetary damages to compensate for such infringement. In the trial for this case held in March 2016, the jury upheld all ten of the asserted claims of the patents-in-suit. The jury then decided that we and Merck are entitled to four percent of $5 billion in past sales of sofosbuvir. Gilead has stated it would appeal the jury’s finding of validity. In the meantime, Gilead asserted two additional non-jury defenses: waiver and unclean hands. Although the judge rejected the waiver defense, she granted Gilead’s motion claiming that the patents are unenforceable against it under the doctrine of unclean hands. We believe this ruling is contrary to the relevant law and the facts of the case. Accordingly, in July 2016, together with Merck we appealed the decision to the Court of Appeals for the Federal Circuit. Gilead cross-appealed on the issue of validity. Briefing on the appeals is now complete and oral arguments were held in February 2018. Under our agreement with Merck, Merck is responsible for the costs of this suit.

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

Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol “IONS.” The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sale prices reported by The Nasdaq Global Select Market. These prices do not include retail markups, markdowns or commissions.

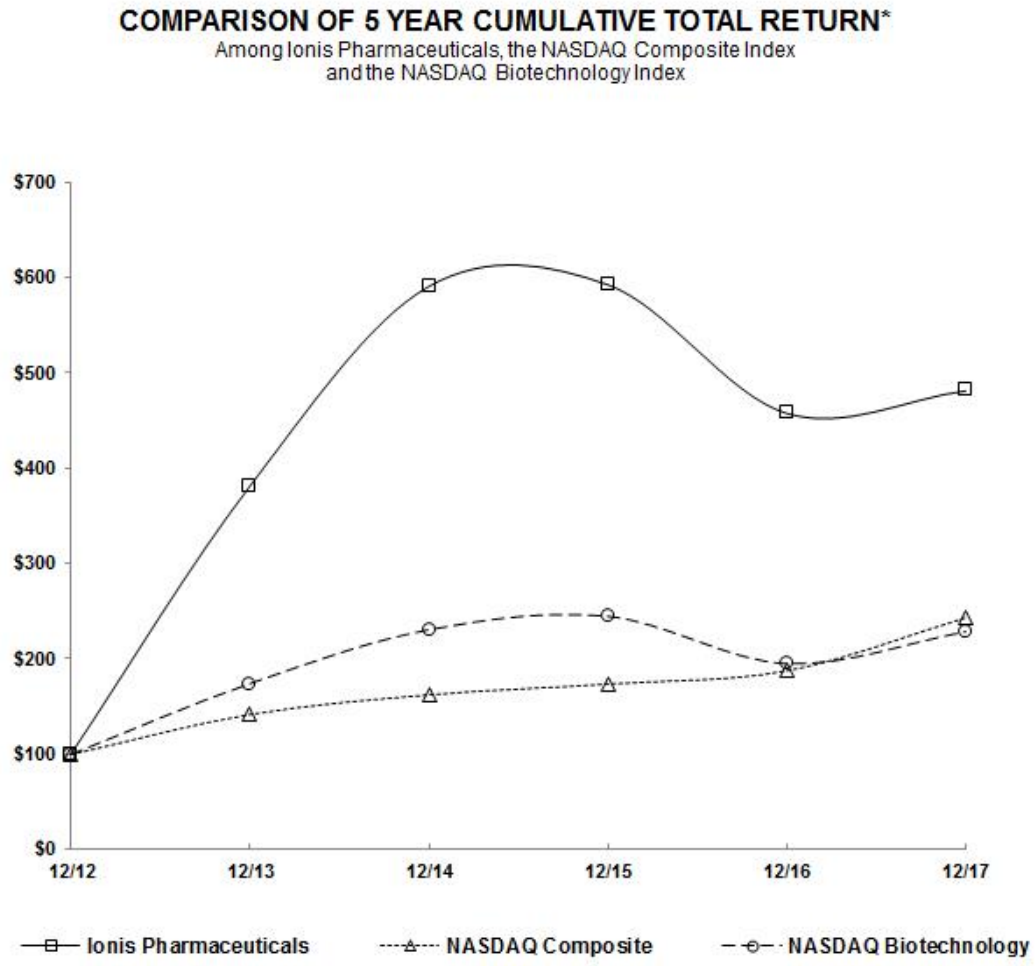
	HIGH	LOW
2017		
First Quarter	$ 56.91	$ 37.29
Second Quarter	$ 55.73	$ 37.26
Third Quarter	$ 60.01	$ 43.75
Fourth Quarter	$ 65.51	$ 50.02
2016		
First Quarter	$ 62.68	$ 30.93
Second Quarter	$ 46.75	$ 19.59
Third Quarter	$ 40.82	$ 23.26
Fourth Quarter	$ 57.00	$ 24.58

As of February 20, 2018, there were approximately 560 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.

Set forth below is a table and chart comparing the total return on an indexed basis of $100 invested on December 31, 2012 in our common stock, the Nasdaq Composite Index (total return) and the Nasdaq Biotechnology Index. The total return assumes reinvestment of dividends.

Performance Graph (1)



*$100 invested on December 31, 2012 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-12	Dec-13	Dec-14	Dec-15	Dec-16	Dec-17
Ionis Pharmaceuticals, Inc.	$ 100.00	$ 381.61	$ 591.38	$ 593.20	$ 458.14	$ 481.80
Nasdaq Composite Index	$ 100.00	$ 141.63	$ 162.09	$ 173.33	$ 187.19	$ 242.29
Nasdaq Biotechnology Index	$ 100.00	$ 174.05	$ 230.33	$ 244.29	$ 194.95	$ 228.29

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

Item 6. Selected Financial Data

This selected financial data should be read in conjunction with our audited consolidated financial statements and accompanying notes and Management's Discussion and Analysis of Financial Condition and Results of Operations included elsewhere in this Annual Report on Form 10-K. Our historical consolidated financial information may not be indicative of our future

performance. Set forth below are our selected consolidated financial data (in thousands, except per share amounts):

	Years Ended December 31,				
	2017	2016	2015	2014	2013
Consolidated Statement of Operations Data:					
Revenue	$ 507,666	$ 346,620	$ 283,703	$ 214,161	$ 147,285
Research, development and patent expenses	$ 374,644	$ 344,320	$ 322,292	$ 241,751	$ 184,033
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (5,970)	$ (86,556)	$ (88,278)	$ (38,984)	$ (60,644)
Basic net income (loss) per share attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 0.08	$ (0.72)	$ (0.74)	$ (0.33)	$ (0.55)
Diluted net income (loss) per share attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 0.08	$ (0.72)	$ (0.74)	$ (0.33)	$ (0.55)
Shares used in computing basic net income (loss) per share	124,016	120,933	119,719	117,691	110,502
Shares used in computing diluted net income (loss) per share	126,098	120,933	119,719	117,691	110,502

	As of December 31,				
	2017	2016	2015	2014	2013
Consolidated Balance Sheet:					
Cash, cash equivalents and short-term investments	$ 1,022,715	$ 665,223	$ 779,183	$ 728,832	$ 656,761
Working capital	$ 943,243	$ 664,148	$ 688,127	$ 721,265	$ 637,698
Total assets	$ 1,322,024	$ 912,467	$ 947,900	$ 946,471	$ 843,267
Long-term debt and other obligations, less current portion	$ 678,564	$ 679,118	$ 598,234	$ 588,896	$ 367,065
Accumulated deficit	$ (1,187,398)	$ (1,181,428)	$ (1,094,872)	$ (1,006,594)	$ (967,610)
Stockholders' equity	$ 418,719	$ 99,565	$ 200,790	$ 257,780	$ 378,390

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

This financial review presents our operating results for each of the three years in the period ended December 31, 2017, and our financial condition at December 31, 2017. Except for the historical information contained herein, the following discussion contains forward-looking statements which are subject to known and unknown risks, uncertainties and other factors that may cause our actual results to differ materially from those expressed or implied by such forward-looking statements. We discuss such risks, uncertainties and other factors throughout this report and specifically under Item 1A of Part I of this report, "Risk Factors." In addition, the following review should be read in conjunction with the information presented in our consolidated financial statements and the related notes to our consolidated financial statements as indexed on page F-1.

Overview

We are leaders in discovering and developing RNA-targeted therapeutics. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics. Using this platform, we have developed a large, diverse and advanced pipeline of potentially first-in-class and/or best-in-class drugs that we believe can provide high value for patients with significant unmet medical needs. In this way, we believe we are fundamentally changing medicine with the goal to transform the lives of those suffering from severe, often life-threatening, diseases.

We made significant progress toward this goal with the commercial launch of SPINRAZA (nusinersen) for the treatment of SMA in pediatric and adult patients. SMA is a leading genetic cause of death in infants marked by progressive, debilitating muscle weakness. SPINRAZA became the first and only approved drug to treat people with SMA and is now the standard of care for this debilitating disease. Our partner, Biogen, is responsible for global commercial activities. In January 2018, Biogen reported that SPINRAZA was available in over 30 global markets. Additionally, Biogen is continuing to purse regulatory approvals for SPINRAZA in countries around the world. In 2017, we earned $113 million in commercial revenue from SPINRAZA royalties. We also earned a $50 million milestone payment for the EU approval of SPINRAZA and a $40 million milestone payment for SPINRAZA pricing approval in Japan.

Our pipeline also contains two near-term, potentially transformative medicines for two different severe and rare diseases, each with significant commercial potential, inotersen and volanesorsen. We believe inotersen has the potential to become the preferred treatment option for many people with hereditary TTR amyloidosis, or hATTR. Our goal is to free these people from the burden of their disease. hATTR is a debilitating, progressive, fatal disease in which patients experience a progressive buildup of amyloid plaque deposits in tissues throughout the body. In May 2017, we reported positive top-line data from our Phase 3 study of inotersen, NEURO-TTR, in patients with hATTR with polyneuropathy. More than half of these patients also have cardiomyopathy. We are advancing inotersen to the market based on the positive data from our NEURO-TTR study. In November 2017, we filed for marketing authorization for inotersen to treat people with hATTR in the U.S. and EU. The Food and Drug Administration, or FDA, accepted the inotersen New Drug Application, or NDA, for Priority Review and set a Prescription Drug User Fee Act, or PDUFA, date of July 6, 2018. The European Medicines Agency, or EMA, also granted accelerated assessment to inotersen, which may reduce standard review time. We are on track in our pre-commercial preparations for a potential launch in mid-2018, if inotersen is approved. Our goals for inotersen are to maximize the commercial potential of the drug, maximize our commercial participation and continue to build our TTR franchise by moving IONIS-TTR-L_{Rx} forward rapidly. We plan to commercialize inotersen in North America ourselves and to seek a commercial partner in other geographic regions.

Akcea Therapeutics, Inc., or Akcea, our affiliate focused on developing and commercializing drugs for serious cardiometabolic diseases caused by lipid disorders, is working closely with us to develop volanesorsen to treat two severe and rare, genetically defined diseases, familial chylomicronemia syndrome, or FCS, and familial partial lipodystrophy, or FPL. FCS and FPL are orphan diseases characterized by severely high triglyceride levels that result in severe, daily symptoms and a high risk of life-threatening pancreatitis. We estimate that FCS and FPL each affect 3,000 to 5,000 people globally. The clinical development program for volanesorsen consists of three Phase 3 studies called APPROACH, BROADEN and COMPASS. In the first quarter of 2017, we and Akcea reported positive Phase 3 data from the APPROACH study in patients with FCS. In December 2016, we and Akcea reported positive results from the Phase 3 COMPASS study in patients with triglycerides above 500 mg/dL. Based on the positive data from our Phase 3 studies, Akcea filed for marketing authorization for volanesorsen in the U.S., EU and Canada in the third quarter of 2017. The FDA set a PDUFA date of August 30, 2018 for volanesorsen and an advisory committee meeting is scheduled for May 10, 2018. Volanesorsen was granted Priority Review in Canada. Akcea is on track in its pre-commercial preparations for a potential launch in mid-2018, if volanesorsen is approved.

In addition to preparing to commercialize volanesorsen, Akcea is focused on developing and commercializing three other clinical-stage drugs for serious cardiometabolic diseases caused by lipid disorders: AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}, each of which could potentially treat multiple patient populations. Moving these drugs into Akcea allows us to retain substantial value from them and ensures our core focus remains on innovation. Akcea completed its initial public offering, or IPO, and a concurrent private placement with Novartis in July 2017, raising over $180 million in net proceeds. As a result of Akcea's IPO and as of February 2018, we owned approximately 68 percent of Akcea.

We are addressing a broad spectrum of diseases that affect millions of people, such as cardiovascular disease, clotting disorders, Alzheimer's and Parkinson's disease. We also are addressing rare diseases, such as acromegaly, amyotrophic lateral sclerosis, beta-thalassemia and Huntington's disease. We are continuing to advance our mid-stage drugs in development, which have the potential to enter late-stage clinical development and progress toward the market over the next several years, like IONIS-HTT_{Rx}. IONIS-HTT_{Rx} is the first drug in clinical development to target the cause of Huntington's disease, or HD, by reducing the production of toxic mutant huntingtin, or mHTT, protein. In December 2017, following successful completion of the Phase 1/2 study in which IONIS-HTT_{Rx} demonstrated dose-dependent reductions of the mHTT protein in patients with HD, Roche licensed IONIS-HTT_{Rx} for $45 million. We plan to report data from this Phase 1/2 study in early 2018. We have also initiated an open-label extension, or OLE, study for people who participated in the Phase 1/2 study. Roche is now responsible for all IONIS-HTT_{Rx} development, regulatory and commercialization activities and costs.

We have established alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our drugs, advancing our technology and preparing to commercialize our products. Our partners bring substantial resources and expertise that augment and build upon our internal capabilities. We have strategic partnerships with Biogen and AstraZeneca through which we can broadly expand our drug discovery efforts to new disease targets in specific therapeutic areas. We also have partnerships with Bayer, GSK, Janssen, Novartis and Roche. Each of these companies brings significant expertise and global resources to develop and potentially commercialize the drugs under these partnerships. Lastly, we also work with a group of companies that can develop our drugs and utilize our technologies outside our primary areas of focus. We refer to these companies as satellite companies.

Through our partnerships, we have created a broad and sustaining base of research and development, or R&D, revenue in the form of license fees, upfront payments and milestone payments while spending prudently to advance our pipeline and technology. Our R&D revenue has consistently grown year over year since 2011. In 2017, we earned $386 million in R&D revenue. Moreover, we have the potential to earn over $13 billion in future milestone payments and licensing fees from our current partnerships. We also have the potential to share in the future commercial success of our inventions and drugs resulting from our partnerships through royalty arrangements. In late 2016, we began adding commercial revenue from SPINRAZA royalties to our existing R&D revenue base. Looking forward, we have the potential to increase our commercial revenue from SPINRAZA royalties from the continued growth we expect in the U.S., EU and in other markets globally. We also have the potential to further increase our commercial revenue with volanesorsen and inotersen. We believe we have the key elements in place to achieve sustained, long-term financial growth, with multiple drivers of revenue; a mature, broad and rapidly-advancing clinical pipeline; a partnership strategy that leverages our partner resources; and an innovative drug discovery technology platform that we continue to deploy across a range of therapeutic areas to address both rare and large patient populations.

Financial Highlights

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

	2017	2016	2015
Total revenue	$ 507,666	$ 346,620	$ 283,703
Total operating expenses	$ 483,132	$ 392,936	$ 359,465
Income (loss) from operations	$ 24,534	$ (46,316)	$ (75,762)
Net loss	$ (17,296)	$ (86,556)	$ (88,278)
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (5,970)	$ (86,556)	$ (88,278)
Cash, cash equivalents and short-term investments	$1,022,715	$ 665,223	$ 779,183

We had a net loss attributable to our common stockholders of $6 million for 2017, compared to $87 million for 2016. Our net loss improved significantly due to the substantial revenue we earned in 2017. During 2017, we added $113 million of commercial revenue from SPRINRAZA royalties. Additionally, we earned R&D revenue of $386 million, including $90 million in milestone payments related to SPINRAZA, a nearly 20 percent increase over 2016.

Our operating expenses for 2017 were $483 million, and increased compared to $393 million for 2016. The increase in operating expenses was primarily due to higher SG&A expenses as we prepare to commercialize volanesorsen and inotersen in 2018. Our SG&A expenses also increased in 2017 compared to 2016 because of fees we owed under our in-licensing agreements related to SPINRAZA. Additionally, stock-based compensation expense increased year over year primarily due to Akcea stock option grants made to new employees as Akcea continues to build out its organization and additional stock option and RSU grants under the Ionis plan. During each of the years above, we were conducting several Phase 3 studies for SPINRAZA, volanesorsen and inotersen along with advancing numerous earlier-stage drugs. We are projecting an increase in our operating expenses for 2018, compared to 2017 primarily due to the cost of preparing for the launch of inotersen and volanesorsen.

During 2017, we received more than $580 million in payments from our partners, primarily from Novartis, Bayer and Biogen reflecting the successes of our partnered programs and drugs. In addition to cash and revenue, our partners provide expertise and additional resources, which we believe will maximize the commercial value of our partnered drugs. Additionally, our 2017 cash balance increased from the proceeds Akcea received from its IPO and Novartis' concurrent strategic investment. We believe our strong financial position should enable us to continue to execute on our corporate goals throughout 2018 and beyond.

Business Segments

In 2015, we began reporting our financial results in two reportable segments, Ionis Core, and Akcea Therapeutics. Segment income (loss) from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class or best-in-class drugs for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy and includes multiple streams of revenue including license fees, milestone payments and royalties, among others.

Akcea Therapeutics is a late-stage biopharmaceutical company focused on developing and commercializing drugs to treat people with serious cardiometabolic diseases caused by lipid disorders. Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea's stock. After Akcea's IPO, we owned approximately 68 percent of Akcea. We did not change our reportable segments as a result of Akcea's IPO.

Critical Accounting Policies

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 policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment.

The following are our significant accounting policies, 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 proper valuation of investments in marketable securities;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimating the impact of the Tax Act and our net deferred income tax asset valuation allowance;
- Determining the fair value of convertible debt without the conversion feature; and
- Valuing premiums under our and Akcea's Novartis collaboration.

Descriptions of these critical accounting policies follow.

Additionally, in January 2018, we adopted the new revenue recognition accounting guidance. As a result, our critical accounting policy for revenue recognition and associated deferred revenue will be updated in our 2018 consolidated financial statements. We are adopting the new standard on a retrospective basis, which means that starting with our first quarter financial statements for 2018 we will begin showing all periods presented using the new standard. The primary impact to our revenue relates to when we recognize milestone payments. Through 2017 under the existing accounting guidance, we recognized milestone payments we earned for performing R&D activities in full when achieved. Under the new guidance starting in 2018, we will now amortize those milestone payments over the period of time we are obligated to perform R&D activities for our partners. For example, in 2017 we initiated a Phase 1/2a clinical study of IONIS-MAPT$_{Rx}$ in patients with mild AD. We earned a $10 million milestone payment from Biogen related to the initiation of this study. In 2017, we recognized the entire $10 million as revenue. Under the new standard, we will recognize this milestone payment over the period we are providing R&D services for Biogen. We will continue to recognize milestone payments we earn based on our partner's activities in full when the milestone is achieved. For example, in 2017 we earned a $50 million milestone payment from Biogen for the EU approval of SPINRAZA. Under both the new and old standard, we account for this milestone payment the same by recognizing the entire amount upon achievement of the event.

Revenue Recognition

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 often enter into agreements to license and sell our technology on an exclusive or non-exclusive basis in exchange for upfront fees, license fees, milestone payments and/or royalties. We generally recognize as revenue immediately license payments with stand-alone value when the license is delivered and we are reasonably assured of collecting the resulting receivable. We recognize royalty revenue in the period in which the counterparty sells the related product, unless we are unable to obtain information to estimate the royalty. For example, in 2017 we recorded SPINRAZA royalty revenue of $112.5 million.

Research and development revenue under collaborative agreements

Arrangements with multiple deliverables

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services, and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable.

Amendments to agreements

From time to time we amend our collaboration agreements. For these agreements, before we identify our deliverables and allocate consideration to each unit of accounting, we must determine if the amendment should be accounted for as a separate agreement, or if the amendment and any undelivered elements for the original agreement should be accounted for as a single new arrangement.

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 patients 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, there was a substantial increase in the consideration we are eligible to receive and a significant change in the deliverables we will provide to Bayer. As a result, we concluded that the amendment should be evaluated with the undelivered elements of the original agreement as a single new arrangement. Therefore, we evaluated our original and 2017 amended agreements with Bayer together to determine our deliverables. We concluded that the 2017 amendment did not impact the items we already delivered to Bayer.

Identifying deliverables and units of accounting

We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to our customer, we account for the deliverables as separate units of accounting. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a stand-alone basis. For example, our 2017 amended agreement with Bayer has multiple elements. We evaluated the deliverables in this arrangement when we entered into the 2017 amended agreement and determined that certain of the deliverables have stand-alone value. Below is a list of the three units of accounting under our 2017 amended agreement:

- The exclusive license we granted to Bayer to develop and commercialize IONIS-FXI-L$_{Rx}$ for the treatment of thrombosis;
- The development services we agreed to perform for IONIS-FXI-L$_{Rx}$ and IONIS-FXI$_{Rx}$; and
- The remaining undelivered IONIS-FXI$_{Rx}$ API that was part of the original agreement.

We determined that each of these three units of accounting have stand-alone value. The license we granted to Bayer has stand-alone value because it gives Bayer the exclusive right to develop IONIS-FXI-L$_{Rx}$ or to sublicense its rights. The development services and the remaining undelivered supply of API each have stand-alone value because Bayer or another third party could provide these items without our assistance.

Measurement and allocation of arrangement consideration

Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees and royalties on product sales. We initially allocate the amount of consideration that is fixed and determinable at the time the agreement is entered into and exclude contingent consideration. We allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. We use the following hierarchy of values to estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BESP. BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

We determined that the allocable arrangement consideration for the Bayer 2017 amended agreement was $76.3 million, comprised of the $75 million we received as part of the amendment and the remaining amount of the $100 million upfront payment we had not yet recognized into revenue, related to the undelivered API. We allocated the consideration based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation specialist to assist us with determining BESP. We estimated the selling price of the license granted for IONIS-FXI-L_{Rx} by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for IONIS-FXI-L_{Rx}. We then discounted the projected income to present value. The significant inputs we used to determine the projected income of the license included:

- Estimated future product sales;
- Estimated royalties on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- Income taxes; and
- An appropriate discount rate.

We estimated the selling price of the development services by using our internal estimates of the cost to perform the specific services and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform the development services. The significant inputs we used to determine the selling price of the development services included:

- The number of internal hours 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 BESP of the services we will perform and the API we will deliver in our 2017 amended Bayer transaction, accounting guidance required us to include a markup for a reasonable profit margin.

Based on the units of accounting under the 2017 amended agreement, we allocated the $76.3 million of allocable consideration as follows:

- $64.9 million to the IONIS-FXI-L_{Rx} exclusive license;
- $11.0 million for development services for IONIS-FXI-L_{Rx} and IONIS-FXI_{Rx}; and
- $0.4 million for the remaining delivery of IONIS-FXI_{Rx} API.

Assuming a constant selling price for the other elements in the arrangement, if there was an assumed 10 percent increase or decrease in the estimated selling price of the IONIS-FXI-L_{Rx} license, we determined that the revenue we would have allocated to the IONIS-FXI-L_{Rx} license would change by approximately one percent, or $0.7 million, from the amount we recorded.

Timing of revenue recognition

We recognize revenue as we deliver each item under the arrangement and the related revenue is realizable and earned. For example, we recognized revenue for the exclusive license we granted Bayer for IONIS-FXI-L_{Rx} in the first quarter of 2017 because that was when we delivered the license. We also recognize revenue over time as we provide services. Our collaborative agreements typically include a research and/or development project plan outlining the activities the agreement requires each party to perform during the collaboration. We estimate our period of performance at the inception of the agreement when the agreements we enter into do not clearly define such information. We then recognize revenue from development services ratably over such period. In certain instances, the period of performance may change as the development plans for our drugs progress. If our estimates and judgments change over the course of our collaboration agreements, it may affect the timing and amount of revenue that we recognize in future periods. We recognize any changes in estimates on a prospective basis.

The following are the periods over which we are recognizing revenue for each of our units of accounting under our 2017 amended Bayer agreement:

- We recognized the portion of the consideration attributed to the IONIS-FXI-L_{Rx} license in the first quarter of 2017 because we delivered the license and earned the revenue;
- We are recognizing the amount attributed to the development services for IONIS-FXI-L_{Rx} and IONIS-FXI_{Rx} over the period of time we are performing the services; and
- We are recognizing the amount attributed to the remaining API supply as we deliver it to Bayer.

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 they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, in the first quarter of 2017, we and Akcea entered into two separate agreements with Novartis at the same time: a collaboration agreement and a SPA.

Akcea entered into a collaboration agreement with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the collaboration agreement, Akcea received a $75 million upfront payment. For each drug, Akcea is responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the FDA and delivering API. Under the collaboration agreement, Novartis has an exclusive option to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. If Novartis exercises an option for one of these drugs, Novartis will pay Akcea a $150 million license fee and will assume all further global development, regulatory and commercialization activities and costs for the licensed drug. Akcea is also eligible to receive a development milestone payment, milestone payments if Novartis achieves pre-specified regulatory milestones, commercial milestones and tiered royalties on net sales from each drug under the collaboration.

Under the SPA, Novartis purchased 1.6 million shares of Ionis' common stock for $100 million in the first quarter of 2017 and paid a premium over the weighted average trading price at the time of purchase. Additionally, the SPA required Novartis to purchase $50 million of Akcea's common stock in a concurrent private placement with Akcea's IPO in July 2017.

We evaluated the Novartis agreements to determine whether we should treat the agreements separately or as a single arrangement. We considered that the agreements were negotiated concurrently and in contemplation of one another. Additionally, the same individuals were involved in the negotiations of both agreements. Based on these facts and circumstances, we concluded that we should treat both agreements as a single arrangement and evaluate the provisions of the agreements on a combined basis. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements for further discussion of the accounting treatment for the Novartis collaboration.

Milestone payments

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and/ or commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraphs.

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds that interact with specific genes that are good targets for drug discovery. From these research efforts, we hope to identify a development candidate. The designation of a development candidate is the start of the development stage, which is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans.

During the first step of the development stage, we or our partners study our drugs in Investigational New Drug, or IND,-enabling studies, which are animal studies intended to support an IND application and/or the foreign equivalent. An approved IND allows us or our partners to study our development candidate in humans. If the regulatory agency approves the IND, we or our partners initiate a Phase 1 clinical trial in which we typically enroll a small number of healthy volunteers to ensure the development candidate is safe for use in patients. If we or our partners determine that a development candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger studies in patients with the primary intent of determining the preliminary efficacy and safety of the development candidate.

The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing authorization from the FDA and/or foreign equivalents. Phase 3 studies typically involve larger numbers of patients and can take up to several years to complete.

If the data gathered during the Phase 3 trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA and/or its foreign equivalents for marketing authorization. This stage of the drug's life-cycle is the regulatory stage.

If the FDA or a foreign equivalent grants marketing authorization for a drug, it moves into the commercialization stage. During this stage we or our partner will market and sell the drug to patients. Although our partner may ultimately be responsible for marketing and selling a partnered drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow us or our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

Generally, the milestone events contained in our partnership agreements coincide with the progression of our drugs from development, to marketing authorization and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately selling it for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

Development milestones in our partnerships may include the following types of events:

- Designation of a development candidate. Following the designation of a development candidate, IND-enabling animal studies for a new development candidate generally take 12 to 18 months to complete.
- Initiation of a Phase 1 clinical trial. Generally, Phase 1 clinical trials take one to two years to complete.
- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete.
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

Regulatory milestones in our partnerships may include the following types of events:

- Filing of regulatory applications for marketing authorization such as a New Drug Application, or NDA, in the United States or a Marketing Authorization Application, or MAA, in Europe. Generally, it takes six to twelve months to prepare and submit regulatory filings.
- Obtaining marketing authorization in a major market, such as the United States, Europe or Japan. Generally it takes one to two years after an application is submitted to obtain authorization from the applicable regulatory agency.

Commercialization milestones in our partnerships may include the following types of events:

- First commercial sale in a particular market, such as in the United States or Europe.
- Product sales in excess of a pre-specified threshold, such as annual sales exceeding $1 billion. The amount of time to achieve this type of milestone depends on several factors including but not limited to the dollar amount of the threshold, the pricing of the product and the pace at which customers begin using the product.

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment immediately. For our licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with access to new technologies we discover, we have determined that the majority of future development, regulatory and commercialization milestones are substantive. For example, we consider most of the milestones associated with our strategic alliance with Biogen substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. In evaluating if a milestone is substantive we consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or in part on our performance or the occurrence of a specific outcome resulting from our performance;
- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over our estimated period of performance, if any. Further information about our collaborative arrangements can be found in Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Option to license

In several of our collaboration agreements, we provide our partner with an option to obtain a license to one or more of our drugs. When we have a multiple element arrangement that includes an option to obtain a license, we evaluate if the option is a deliverable at the inception of the arrangement. We do not consider the option to be a deliverable if we conclude that it is substantive and not priced at a significant and incremental discount. We consider an option substantive if, at the inception of the arrangement, we are at risk as to whether our collaboration partner will choose to exercise its option to obtain the license. In those circumstances, we do not include the associated license fee in the allocable consideration at the inception of the agreement. Rather, we account for the license fee when our partner exercises its option. For example, during 2017, we earned license fee revenue when three of our partners, Bayer, Janssen and Roche, exercised their options to license three of our drugs, which under the respective agreements we concluded to be substantive options at inception. As a result, in 2017 we recognized the related revenue immediately in research and development revenue under collaborative agreements on our statement of operations as these amounts relate to drugs in development under research and development collaboration arrangements.

Valuation of Investments in Marketable Securities

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 investments as “available-for-sale” and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments. We use the specific identification method to determine the cost of securities sold.

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

Estimated Liability for Clinical Development Costs

We record accrued liabilities related to expenses for which service providers have not yet billed us. These liabilities are for products or services that we have received, specifically related to ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. We have numerous drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. In order to ensure that we have adequately provided for ongoing preclinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires 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.

Estimating the Impact of the Tax Cuts and Jobs Act of 2017 and Our Net Deferred Income Tax Asset Valuation Allowance

On December 22, 2017, the Tax Act was signed into law. The Tax Act makes broad and complex changes to the U.S. tax code. The changes include, but are not limited to, reducing the U.S. federal corporate tax rate from 35 percent to 21 percent, imposing a mandatory one-time transition tax on certain unrepatriated earnings of foreign subsidiaries, introducing bonus depreciation that will allow for full expensing of qualified property, eliminating the corporate alternative minimum tax, or AMT, and changing how existing AMT credits can be realized, and modifying or repealing many business tax deductions and credits.

The SEC staff issued guidance to address the application of U.S. GAAP in situations when a registrant does not have the necessary information available, prepared, or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of the Tax Act.

In accordance with the SEC guidance, the amounts we presented are preliminary and our best estimate of the impact of the Tax Act in the period ending December 31, 2017 based on our understanding of the Tax Act and guidance available as of the date of this filing. We remeasured our existing net U.S. deferred tax assets using the enacted tax rate and other known significant changes to the tax code. This resulted in a total decrease in these assets by $107.3 million which was fully offset by a decrease in our valuation allowance. In addition, we recorded a $7.7 million tax benefit related to our cumulative prior year AMT tax credit carryovers, which are now included as part of a long-term income tax receivable because under the Tax Act, AMT credits are refundable from 2018 through 2021.

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. Valuation allowances are provided when necessary to reduce 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. Estimates of future taxable income are based 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 have incurred historical financial statement losses and as a result we have a full valuation allowance recorded against our net deferred tax assets. We regularly assess the future realization of our net deferred tax assets and will reduce the valuation allowance in any such period in which we determine that all, or a portion, of our deferred tax assets are 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.

Convertible Debt

We account for our convertible debt instruments 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. We determine the carrying amount of the liability component by measuring the fair value of similar debt instruments that do not have the conversion feature. If a similar debt instrument does not exist, we estimate the fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities. Determining the fair value of the debt component requires the use of accounting estimates and assumptions. These estimates and assumptions are judgmental in nature and could have a significant impact on the determination of the debt component and the associated non-cash interest expense.

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 the debt at a discount. We are amortizing our debt issuance costs and our 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*, in the Notes to the Consolidated Financial Statements.

Valuation of Premiums under our and Akcea's Novartis Collaboration

During the first quarter of 2017, we valued the premiums under the SPA agreement with Novartis. These premiums included the premium Novartis paid us related to its $100 million purchase of our stock in the first quarter of 2017 and the premium we could have received related to Novartis' potential purchase of our stock. These valuations required us to use level 3 inputs, which we consider to be a critical accounting policy for our results for 2017.

We determined the fair value of the premium we received and the future premium we could have 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 premiums because Novartis received unregistered shares as part of Novartis' $100 million equity purchase and we would have issued unregistered shares to Novartis if it had purchased our common stock. Additionally, for the future potential stock purchase, we estimated the probability of an Akcea IPO. At the inception of the agreements, we calculated the following fair values:

- $28.4 million for the premium paid by Novartis for its purchase of our common stock in the first quarter of 2017; and
- $5.0 million for the potential premium Novartis would have paid if it had purchased our common stock in the future at a premium.

Because Akcea completed its IPO before April 2018, Novartis will not purchase additional shares of Ionis stock. Therefore, this asset no longer had any value and we wrote-off the remaining potential premium Novartis would have paid to us if an Akcea IPO did not occur. We wrote off the amount to other expenses on our consolidated statement of operations during the third quarter of 2017. See further discussion about our valuation of the potential premium in our Fair Value Measurements policy in Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements.

Results of Operations

Years Ended December 31, 2017 and December 31, 2016

Revenue

Total revenue for 2017 was $507.7 million, compared to $346.6 million for 2016. See below for our discussion of the changes in our revenue.

Commercial Revenue

SPINRAZA Royalties

2017 was the first full year in which we earned commercial revenue from SPINRAZA royalties. Commercial revenue from SPINRAZA royalties for 2017 was $112.5 million, compared to $0.9 million in 2016.

Licensing and Other Royalty Revenue

Our revenue from licensing activities and other royalties for 2017 was $9.5 million, compared to $19.8 million for 2016. During 2016 we earned $15 million from Kastle when it acquired the global rights to develop and commercialize Kynamro.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for 2017 was $385.6 million, compared to $325.9 million for 2016. The change in our R&D revenue was primarily due to increased amortization from the upfront payment Akcea received in 2017 from the collaboration with Novartis. Our R&D revenue for 2017 primarily consisted of the following:

- $118 million in milestone payments from Biogen, including $90 million in approval milestone payments for SPINRAZA, $15 million in milestone payments for validating two undisclosed neurological disease targets and $10 million for initiating a Phase 1/2a study of IONIS-MAPT$_{Rx}$;
- $65 million from Bayer for the license of IONIS-FXI-L$_{Rx}$;
- $48 million from Roche primarily for the license of IONIS-HTT$_{Rx}$;
- $10 million from Janssen for the license of IONIS-JBI2-2.5$_{Rx}$ and initiation of a Phase 1 study of IONIS-JBI1-2.5$_{Rx}$:
- $115 million from the amortization of upfront fees; and
- $29.6 million primarily from services we performed for our partners.

Our R&D revenue may fluctuate quarterly based on the nature and timing of payments under agreements with our partners and consists primarily of revenue from the amortization of upfront fees, milestone payments and license fees.

Operating Expenses

Operating expenses for 2017 were $483.1 million, and increased compared to $392.9 million for 2016. Our operating expenses increased year over year principally due to higher SG&A expenses as we prepare to commercialize volanesorsen and inotersen. Our SG&A expenses also increased in 2017 compared to 2016 because of fees we owed under our in-licensing agreements related to SPINRAZA.

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

	Year Ended December 31,	
	2017	**2016**
Ionis Core	$ 305,352	$ 260,233
Akcea Therapeutics	146,332	73,363
Elimination of intercompany activity	(54,527)	(12,768)
Subtotal	397,157	320,828
Non-cash compensation expense related to equity awards	85,975	72,108
Total operating expenses	$ 483,132	$ 392,936

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 is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it.

Research, Development and Patent Expenses

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

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

	Year Ended December 31,	
	2017	**2016**
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 310,123	$ 289,221
Non-cash compensation expense related to equity awards	64,521	55,099
Total research, development and patent expenses	$ 374,644	$ 344,320

For 2017, our research, development and patent expenses were $310.1 million, compared to $289.2 million for 2016. Our research, development and patent expenses increased slightly primarily related to expenses such as regulatory filings, manufacturing initial launch supplies and medical affairs activities in support of inotersen and volanesorsen. If you exclude these expenses, our research, development and patent expenses decreased year-over-year; demonstrating we can prudently manage our research, development and patent expenses, even while advancing and expanding our pipeline, because of the efficiency of antisense technology and the contributions of our partners. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2017	**2016**
Ionis Core	$ 246,390	$ 238,106
Akcea Therapeutics	118,260	63,883
Elimination of intercompany activity	(54,527)	(12,768)
Subtotal	310,123	289,221
Non-cash compensation expense related to equity awards	64,521	55,099
Total research, development and patent expenses	$ 374,644	$ 344,320

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.

As we continue to advance our antisense technology, we are investing in our drug discovery programs to expand our and our partners' drug pipelines. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs and contribute to the advancement of the science by funding core antisense technology research.

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

	Year Ended December 31,	
	2017	2016
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 56,160	$ 51,028
Non-cash compensation expense related to equity awards	15,203	13,589
Total antisense drug discovery expenses	$ 71,363	$ 64,617

Antisense drug discovery expenses for 2017 were $56.2 million and were slightly higher compared to $51.0 million for 2016, due to expenses we incurred related to advancing our early stage research programs. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Year Ended December 31,	
	2017	2016
SPINRAZA	$ 10,996	$ 43,868
Volanesorsen	22,524	26,285
Inotersen	24,880	22,939
Other antisense development projects	70,009	42,999
Development overhead expenses	43,784	39,398
Total antisense drug development, excluding non-cash compensation expense related to equity awards	172,193	175,489
Non-cash compensation expense related to equity awards	25,737	20,116
Total antisense drug development expenses	$ 197,930	$ 195,605

Antisense drug development expenses were $172.2 million for 2017 and were essentially flat compared to $175.5 million for 2016. As we projected, the expenses for SPINRAZA and volanesorsen declined in 2017. Specifically, we have transitioned all further development of SPINRAZA to Biogen and we are finishing our Phase 3 volanesorsen trial in people with FCS. Additionally, we completed our Phase 3 inotersen trial in people with hATTR with polyneuropathy. Our 2017 expenses included $4.8 million of expenses related to regulatory filing activities for volanesorsen and inotersen. Additionally, during 2017, we made investments in our other antisense development projects, including AKCEA-APO(a)-L_{Rx} and IONIS-FXI$_{Rx}$. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2017	2016
Ionis Core	$ 122,163	$ 132,418
Akcea Therapeutics	98,425	43,071
Elimination of intercompany activity	(48,395)	—
Subtotal	172,193	175,489
Non-cash compensation expense related to equity awards	25,737	20,116
Total antisense drug development expenses	$ 197,930	$ 195,605

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 products 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 product. Although we may characterize a product 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 products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products 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 product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous drugs in preclinical and early stage clinical research, the fluctuations in expenses from drug to drug, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related costs.

Medical Affairs

Our medical affairs function is responsible for performing further research regarding our drugs to ensure appropriate medical use. In addition, members of our medical affairs team educate the medical community about the diseases our drugs are designed to treat.

Expenditures in our medical affairs function include personnel costs and outside services.

Our medical affairs expenses were as follows (in thousands):

	Year Ended December 31,	
	2017	2016
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 9,097	$ 3,568
Non-cash compensation expense related to equity awards	2,588	1,264
Total medical affairs expenses	$ 11,685	$ 4,832

Medical affairs expenses were $9.1 million for 2017 and were higher compared to $3.6 million for 2016. The increase was primarily due to the build-out of our medical affairs teams and associated activities to educate the medical community on FCS and hATTR. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2017	2016
Ionis Core	$ 1,771	$ —
Akcea Therapeutics	7,326	3,568
Subtotal	9,097	3,568
Non-cash compensation expense related to equity awards	2,588	1,264
Total medical affairs expenses	$ 11,685	$ 4,832

Manufacturing and Operations

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

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

	Year Ended December 31,	
	2017	2016
Manufacturing and operations expenses, excluding non-cash compensation expense related to equity awards	$ 43,526	$ 30,148
Non-cash compensation expense related to equity awards	6,904	6,113
Total manufacturing and operations expenses	$ 50,430	$ 36,261

Manufacturing and operations expenses were $43.5 million for 2017 and were higher compared to $30.1 million for 2016. $11 million of the increase in manufacturing expenses was related to volanesorsen and inotersen to prepare for the planned launches in mid-2018, if approved. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2017	2016
Ionis Core	$ 39,098	$ 27,341
Akcea Therapeutics	10,440	15,455
Elimination of intercompany activity	(6,012)	(12,648)
Subtotal	43,526	30,148
Non-cash compensation expense related to equity awards	6,904	6,113
Total manufacturing and operations expenses	$ 50,430	$ 36,261

R&D Support

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

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

	Year Ended December 31,	
	2017	2016
Personnel costs	$ 11,432	$ 11,560
Occupancy	8,236	7,891
Patent expenses	2,095	3,945
Depreciation and amortization	249	245
Insurance	1,735	1,344
Other	5,400	4,003
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	29,147	28,988
Non-cash compensation expense related to equity awards	14,089	14,017
Total R&D support expenses	$ 43,236	$ 43,005

R&D support expenses for 2017 were $29.1 million and were flat compared to $29.0 million for 2016. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2017	2016
Ionis Core	$ 27,198	$ 27,319
Akcea Therapeutics	2,069	1,789
Elimination of intercompany activity	(120)	(120)
Subtotal	29,147	28,988
Non-cash compensation expense related to equity awards	14,089	14,017
Total R&D support expenses	$ 43,236	$ 43,005

Selling, General and Administrative Expenses

Selling, general and administrative expenses include costs associated with the pre-commercialization activities for our drugs and costs to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of pre-commercialization, 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 owed under our in-licensing agreements related to SPINRAZA in our SG&A expenses.

The following table sets forth information on selling, general and administrative expenses (in thousands):

	Year Ended December 31,	
	2017	2016
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 87,034	$ 31,607
Non-cash compensation expense related to equity awards	21,454	17,009
Total selling, general and administrative expenses	$ 108,488	$ 48,616

Selling, general and administrative expenses were $87.0 million for 2017 and significantly increased compared to $31.6 million for 2016. The increase in SG&A expenses was principally due to the cost of preparing to commercialize volanesorsen and inotersen in mid-2018 and from fees we owed under our in-licensing agreements related to SPINRAZA. We project our expenses will increase if SPINRAZA sales continue to grow and as we continue to prepare to launch inotersen and Akcea continues to prepare to launch volanesorsen. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2017	2016
Ionis Core	$ 58,962	$ 22,127
Akcea Therapeutics	28,072	9,480
Non-cash compensation expense related to equity awards	21,454	17,009
Total selling general and administrative expenses	$ 108,488	$ 48,616

Akcea Therapeutics, Inc.

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

	Year Ended December 31,	
	2017	**2016**
Development and patent expenses	$ 118,260	$ 63,883
General and administrative expenses	28,072	9,480
Total operating expenses, excluding non-cash compensation expense related to equity awards	146,332	73,363
Non-cash compensation expense related to equity awards	17,539	10,149
Total Akcea Therapeutics operating expenses	$ 163,871	$ 83,512

Operating expenses for Akcea were $146.3 million for 2017 and increased compared to $73.4 million for 2016.

$48.4 million of the increase in Akcea's development and patent expenses was for one-time sublicensing expenses related to the Novartis collaboration recorded in the first quarter of 2017. $33.4 million of these expenses were non-cash and the remaining $15 million was paid to us. For each period presented, we allocated a portion of Ionis' R&D support expenses, which are included in development and patent expenses in the table above, to Akcea for work we performed on behalf of Akcea.

Akcea's G&A expenses increased in 2017, compared to 2016, primarily due to Akcea continuing to build its commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen in mid-2018, if approved. During the first quarter of 2017, we and Akcea reported positive results from the APPROACH Phase 3 study of volanesorsen in people with FCS. During the third quarter of 2017, Akcea, working closely with us, filed for marketing approval in the U.S., EU and Canada. For each period presented, we allocated a portion of Ionis' G&A expenses, which were included in Akcea's G&A expenses in the table above, to Akcea for work we performed on Akcea's behalf.

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

Investment Income

Investment income for 2017 was $7.8 million compared to $5.5 million for 2016. Investment income increased primarily due a higher average cash balance and an improvement in the market conditions during 2017 compared to 2016.

Interest Expense

Interest expense for 2017 was $44.8 million, compared to $38.8 million for 2016. The increase was primarily non-cash expense related to amortization of debt issuance costs for our 1 percent notes.

Interest expense includes non-cash amortization of the debt discount and debt issuance costs plus interest expense payable in cash for our 1 percent and 2¾ percent notes, non-cash interest expense related to the long-term financing liability, which was replaced by mortgage debt for our primarily R&D and manufacturing facilities beginning in July 2017 and other miscellaneous debt.

In July 2017, we purchased the building that houses our primary R&D facility and the building that houses our manufacturing facility for $79.4 million and $14.0 million, respectively. As a result of the purchase of our primary R&D facility, we extinguished the financing liability we had previously recorded on our balance sheet. We financed the purchase of the buildings with mortgage debt of $51.3 million with an interest rate of 3.88 percent for our primary R&D facility and mortgage debt of $9.1 million with an interest rate of 4.2 percent for our manufacturing facility. Both mortgages mature in August 2027. The non-cash interest expense for our long-term financing liability was replaced with lower mortgage interest expense.

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

	Year Ended December 31,	
	2017	**2016**
Convertible notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 32,536	$ 25,115
Interest expense payable in cash	7,090	6,684
Non-cash interest expense for long-term financing liability	3,352	6,693
Interest on mortgage for primary R&D and manufacturing facilities	1,103	—
Other	671	303
Total interest expense	$ 44,752	$ 38,795

Loss on Extinguishment of Financing Liability for Leased Facility

We recognized a loss on extinguishment of the financing liability for leased facility of $7.7 million in 2017. The loss represents the difference between the amount we previously recorded as a financing liability for the leased facility and the purchase price we paid for our primary R&D facility in July 2017. This loss was non-cash and nonrecurring.

Early Retirement of Debt

As a result of the debt exchange we completed in December 2016, we recorded a $4.0 million non-cash loss on early retirement of debt, reflecting the early retirement of the majority of our remaining 2¾ percent convertible notes in December 2016. We did not recognize any loss on early retirement of debt in 2017.

Other Expenses

Other expenses were $3.5 million for 2017 and primarily consisted of the previously capitalized fair value of the potential premium we would have received from Novartis if Akcea had not completed its IPO. This expense was non-cash and nonrecurring.

Income Tax Benefit (Expense)

We are subject to U.S. federal, state and foreign taxes. In 2017, we recorded a net income tax benefit of $6.0 million, compared to income tax expense of $2.9 million in 2016. Our tax expense flipped from an expense position in 2016 to a benefit position in 2017 primarily due to a $7.7 million reduction in our valuation allowance. As a result of the Tax Act, we reduced our valuation allowance because we are entitled to receive a tax refund for our cumulative prior year alternative minimum tax credit carryforwards. At December 31, 2017 we retained a full valuation allowance against the net balance of our remaining deferred tax assets.

Net Loss

We had a net loss of $17.3 million for 2017, compared to $86.6 million for 2016. Our net loss improved for 2017 compared to 2016 primarily due to the addition of commercial revenue from SPINRAZA royalties and increased R&D revenue.

Net Operating Loss and Tax Credit Carryforwards

At December 31, 2017, we had federal and California tax net operating loss carryforwards of approximately $561.1 million and $887.1 million, respectively. Our federal tax loss carryforwards begin to expire in 2024. A portion of our California tax loss carryforwards continued to expire in 2017. At December 31, 2017, we also had federal and California research and development tax credit carryforwards of approximately $233.3 million and $56.2 million, respectively. Our Federal research and development tax credit carryforwards will begin to expire in 2018. Our California research and development tax credit carryforwards are available indefinitely.

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

As a result of Akcea's IPO, beginning in July 2017, we no longer own 100 percent of Akcea. From the closing of Akcea's IPO on July 19, 2017 through the end of 2017, we owned approximately 68 percent of Akcea. As a result, we adjusted our financial statements to reflect the portion of Akcea we no longer own, which was 32 percent at December 31, 2017. Accordingly, our consolidated statement of operations now includes a new line called "Net loss attributable to noncontrolling interests in Akcea", our noncontrolling interest in Akcea for 2017 was $11.3 million. We also added a corresponding account to our consolidated balance sheet called "Noncontrolling interest in Akcea Therapeutics, Inc."

Net 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 $6.0 million for 2017, compared to $86.6 million in 2016. Basic and diluted net income per share for 2017 was $0.08 compared to a net loss per share of $0.72 for 2016.

Years Ended December 31, 2016 and December 31, 2015

Revenue

Total revenue for 2016 was $346.6 million compared to $283.7 million for 2015.

Commercial Revenue

SPINRAZA Royalties

SPINRAZA was approved by the FDA in December 2017. Commercial revenue from SPINRAZA royalties for 2016 was $0.9 million.

Licensing and Other Royalty Revenue

Our revenue from licensing activities and royalties for 2016 was $19.8 million, compared to $2.3 million for 2015. Our revenue from licensing and royalties for 2016 primarily consisted of the $15 million we earned from Kastle when it acquired the global rights to develop and commercialize Kynamro.

Research and Development Revenue Under Collaborative Agreements

Research and development revenue under collaborative agreements for 2016 was $325.9 million compared to $281.4 million for 2015. We earned $115.7 million in milestone payments and $91.2 million when Bayer licensed IONIS-FXI$_{Rx}$ during 2016 compared to milestone payments of $135.0 million in 2015. Our revenue in 2016 was primarily comprised of:

- $170 million from Biogen for FDA approval, licensing and advancing the Phase 3 program for SPINRAZA;
- $53 million from AstraZeneca for advancing and licensing IONIS-KRAS-2.5$_{Rx}$ and selecting IONIS-AZ4-2.5-L$_{Rx}$ to move into development;
- $15 million from Janssen for licensing IONIS-JBI1-2.5$_{Rx}$ and selecting an additional development candidate;
- $7.5 million from Biogen for advancing IONIS-SOD1$_{Rx}$, IONIS-BIIB4$_{Rx}$ and IONIS-BIIB6$_{Rx}$;
- $61 million from the amortization of upfront fees; and
- $19.4 million primarily from the manufacturing services we performed for our partners.

Operating Expenses

Operating expenses for 2016 were $392.9 million, and increased compared to $359.5 million for 2015. The increase in operating expenses was primarily due to:

- During 2016, we were conducting five Phase 3 studies and three open-label extension studies for SPINRAZA, inotersen and volanesorsen. We completed target enrollment in four of these Phase 3 studies at the end of 2015, and as a result, these studies were in their most expensive stage during 2016.
- Akcea's operating expenses increased as it continued to build its commercial infrastructure and advance the pre-commercialization activities necessary to successfully launch volanesorsen, if approved for marketing.
- Our non-cash compensation expense related to equity awards increased due to an increase in the exercise price of the stock options we have granted over the past several years.

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

	Year Ended December 31,	
	2016	**2015**
Ionis Core	$ 260,233	$ 256,674
Akcea Therapeutics	73,363	46,252
Elimination of intercompany activity	(12,768)	(2,775)
Subtotal	320,828	300,151
Non-cash compensation expense related to equity awards	72,108	59,314
Total operating expenses	$ 392,936	$ 359,465

Research, Development and Patent Expenses

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

	Year Ended December 31,	
	2016	**2015**
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 289,221	$ 278,654
Non-cash compensation expense related to equity awards	55,099	43,638
Total research, development and patent expenses	$ 344,320	$ 322,292

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

	Year Ended December 31,	
	2016	**2015**
Ionis Core	$ 238,106	$ 240,061
Akcea Therapeutics	63,883	41,368
Elimination of intercompany activity	(12,768)	(2,775)
Subtotal	289,221	278,654
Non-cash compensation expense related to equity awards	55,099	43,638
Total research, development and patent expenses	$ 344,320	$ 322,292

For 2016, total research, development and patent expenses were $289.2 million, compared to $278.7 million for 2015, and were slightly higher primarily due to the progression of our drugs in Phase 3 development. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Discovery

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

	Year Ended December 31,	
	2016	2015
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 51,028	$ 49,331
Non-cash compensation expense related to equity awards	13,589	11,914
Total antisense drug discovery expenses	$ 64,617	$ 61,245

Antisense drug discovery expenses for 2016 were $51.0 million and were slightly higher compared to $49.3 million for 2015, All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Year Ended December 31,	
	2016	2015
SPINRAZA	$ 43,868	$ 35,164
Volanesorsen	26,285	21,348
Inotersen	22,939	19,560
Other antisense development products	42,999	59,599
Development overhead expenses	39,398	36,117
Total antisense drug development, excluding non-cash compensation expense related to equity awards	175,489	171,788
Non-cash compensation expense related to equity awards	20,116	16,108
Total antisense drug development expenses	$ 195,605	$ 187,896

Antisense drug development expenditures were $175.5 million for 2016 compared to $171.8 million for 2015. Expenses in 2016 were slightly higher compared to 2015 primarily due to the progression of our drugs in Phase 3 development. As drugs move forward to more advanced stages of development, including into larger, longer clinical studies, the costs of development increase. Our other antisense development project expenses declined in 2016, compared to 2015, primarily due to completing the FOCUS FH Phase 3 study of Kynamro in 2015 and our shift to LICA drugs, which were in less expensive stages of development. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2016	2015
Ionis Core	$ 132,418	$ 137,092
Akcea Therapeutics	43,071	34,696
Non-cash compensation expense related to equity awards	20,116	16,108
Total antisense drug development expenses	$ 195,605	$ 187,896

Medical Affairs

Our medical affairs expenses were as follows (in thousands):

	Year Ended December 31,	
	2016	2015
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 3,568	$ 429
Non-cash compensation expense related to equity awards	1,264	100
Total medical affairs expenses	$ 4,832	$ 529

Medical affairs expenses were $3.6 million for 2016 and were higher compared to $0.4 million for 2015. The increase was primarily due to the build-out of our medical affairs team and associated activities to educate the medical community on FCS. All amounts exclude non-cash compensation expense related to equity awards. All of our medical affairs expenses for 2016 and 2015 related to our Akcea segment.

Manufacturing and Operations

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

	Year Ended December 31,	
	2016	2015
Manufacturing and operations expenses, excluding non-cash compensation expense related to equity awards	$ 30,148	$ 28,588
Non-cash compensation expense related to equity awards	6,113	4,563
Total manufacturing and operations expenses	$ 36,261	$ 33,151

Manufacturing and operations expenses for 2016 were $30.1 million and were slightly higher compared to $28.6 million for 2015. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2016	2015
Ionis Core	$ 27,341	$ 25,632
Akcea Therapeutics	15,455	5,611
Elimination of intercompany activity	(12,648)	(2,655)
Subtotal	30,148	28,588
Non-cash compensation expense related to equity awards	6,113	4,563
Total manufacturing and operations expenses	$ 36,261	$ 33,151

R&D Support

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

	Year Ended December 31,	
	2016	2015
Personnel costs	$ 11,560	$ 10,210
Occupancy	7,891	7,854
Patent expenses	3,945	2,785
Depreciation and amortization	245	2,911
Insurance	1,344	1,320
Other	4,003	3,438
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	28,988	28,518
Non-cash compensation expense related to equity awards	14,017	10,953
Total R&D support expenses	$ 43,005	$ 39,471

R&D support expenses for 2016 were $29.0 million, and were essentially flat compared to $28.5 million for 2015. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2016	2015
Ionis Core	$ 27,319	$ 28,005
Akcea Therapeutics	1,789	633
Elimination of intercompany activity	(120)	(120)
Subtotal	28,988	28,518
Non-cash compensation expense related to equity awards	14,017	10,953
Total R&D support expenses	$ 43,005	$ 39,471

General and Administrative Expenses

The following table sets forth information on general and administrative expenses (in thousands):

	Year Ended December 31,	
	2016	2015
General and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 31,607	$ 21,497
Non-cash compensation expense related to equity awards	17,009	15,676
Total general and administrative expenses	$ 48,616	$ 37,173

General and administrative expenses for 2016 were $31.6 million and increased compared to $21.5 million for 2015 primarily due to expenses associated with Akcea building its organization. All amounts exclude non-cash compensation expense related to equity awards.

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

	Year Ended December 31,	
	2016	2015
Ionis Core	$ 22,127	$ 16,613
Akcea Therapeutics	9,480	4,884
Non-cash compensation expense related to equity awards	17,009	15,676
Total general and administrative expenses	$ 48,616	$ 37,173

Akcea Therapeutics, Inc.

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

	Year Ended December 31,	
	2016	2015
Development and patent expenses	$ 63,883	$ 41,368
General and administrative expenses	9,480	4,884
Total operating expenses, excluding non-cash compensation expense related to equity awards	73,363	46,252
Non-cash compensation expense related to equity awards	10,149	6,496
Total Akcea Therapeutics operating expenses	$ 83,512	$ 52,748

Akcea’s operating expenses were $73.4 million for 2016 and increased compared to $46.3 million for 2015. The increase in expenses was primarily because Akcea was conducting more and later-stage clinical studies in 2016 than it conducted in 2015, including the continuation of the Phase 3 studies for volanesorsen in people with FCS and FPL. In 2016, we began charging Akcea for Ionis’ internal development costs associated with the ongoing work we are performing for Akcea's drugs. For each period presented, we allocated a portion of Ionis' R&D support expenses, which are included in research and development expenses in the table above, to Akcea for work we performed on behalf of Akcea.

Akcea also incurred additional general and administrative costs as it continued to build its organization and advance the pre-commercialization activities necessary to launch volanesorsen, if approved for marketing. For each year presented, we allocated a portion of Ionis' general and administrative expenses, which are included in general and administrative expenses in the table above, to Akcea for work we performed on Akcea’s behalf. All amounts exclude non-cash compensation expense related to equity awards.

Investment Income

Investment income for 2016 totaled $5.5 million compared to $4.4 million for 2015. The increase in investment income was primarily due an improvement in the market conditions during 2016 compared to 2015.

Interest Expense

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

	Year Ended December 31,	
	2016	2015
Convertible notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 25,115	$ 23,208
Interest expense payable in cash	6,684	6,683
Non-cash interest expense for long-term financing liability	6,693	6,665
Other	303	176
Total interest expense	$ 38,795	$ 36,732

Interest expense for 2016 was $38.8 million, and was relatively flat compared to $36.7 million in 2015.

Gain on Investment in Regulus Therapeutics Inc.

In 2015, we recorded a gain on our investment in Regulus of $20.2 million related to our sale of a portion of our Regulus common stock.

Early Retirement of Debt

As a result of the debt exchange we completed in December 2016, we recorded a $4.0 million non-cash loss on early retirement of debt, reflecting the early retirement of the majority of our remaining 2¾ percent convertible notes in December 2016. We did not recognize any loss on early retirement of debt in 2015.

Income Tax Expense (Benefit)

In 2016, we recorded a net tax expense of $2.9 million, compared to $0.4 million in 2015. Our tax expense increased in 2016 compared to 2015 primarily due to the taxable income resulting from our strong financial performance in 2016 and excess tax benefits related to stock-based compensation. Included in our tax expense for 2015 is $4.3 million of tax benefit we recorded in 2015 related to a tax refund we received in 2015 from the State of California Franchise Tax Board related to the California franchise taxes we paid for the tax year ended December 31, 2009.

Net Loss and Net Loss Per Share

Net loss for 2016 was $86.6 million compared $88.3 million for 2015. Basic and diluted net loss per share for the year ended December 31, 2016 was $0.72 compared to $0.74 for 2015. We had a lower net loss in 2016 primarily due to the increase in revenue we earned in 2016 compared to 2015.

Liquidity and Capital Resources

We have financed our operations with revenue primarily from research and development collaborative agreements Beginning in December 2016 we added commercial revenue from SPINRAZA royalties. From our inception through December 31, 2017, we had earned approximately $2.6 billion in revenue. We also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through December 31, 2017, we had raised net proceeds of approximately $1.2 billion from the sale of our equity securities, not including the $182.4 million Akcea received in net proceeds from its IPO in July 2017. Additionally, we had borrowed approximately $1.4 billion under long-term debt arrangements to finance a portion of our operations over the same time period.

At December 31, 2017, we had cash, cash equivalents and short-term investments of $1.0 billion and stockholders' equity of $418.7 million. In comparison, we had cash, cash equivalents and short-term investments of $665.2 million and stockholders' equity of $99.6 million at December 31, 2016. During 2017, we received more than $580 million in payments from our partners, primarily from Novartis, Bayer and Biogen. Additionally, our cash balance at December 31, 2017 included the proceeds from Akcea's IPO and Novartis' strategic investment received in the third quarter of 2017.

In July 2017, we purchased two buildings that house our primary R&D facility and our manufacturing facility for $79.4 million and $14.0 million, respectively. In conjunction with the purchase of the buildings we obtained a $51.4 million mortgage for our primary R&D facility and a $9.1 million mortgage for our manufacturing facility. Both mortgages mature in August 2027. We expect these transactions will result in cash and expense savings for us.

At December 31, 2017, we had consolidated working capital of $943.2 million compared to $664.1 million at December 31, 2016. Working capital increased in 2017 primarily due to the increase in our cash, cash equivalents and short-term investments as a result of the substantial payments we received from partners and Akcea's IPO during 2017.

As of December 31, 2017, our debt and other obligations totaled $759.8 million compared to $774.2 million at December 31, 2016.

The following table summarizes our contractual obligations as of December 31, 2017. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
Convertible senior notes (principal and interest payable)	$ 712.9	$ 6.9	$ 13.7	$ 692.3	$ —
Building mortgage payments	$ 83.2	$ 2.4	$ 4.8	$ 5.1	$ 70.9
Financing arrangements (principal and interest payable)	$ 13.0	$ 0.3	$ 12.7	$ —	$ —
Other obligations (principal and interest payable)	$ 1.1	$ 0.1	$ 0.1	$ 0.1	$ 0.8
Operating leases	$ 2.1	$ 0.9	$ 1.1	$ 0.1	$ —
Total	$ 812.3	$ 10.6	$ 32.4	$ 697.6	$ 71.7

Our contractual obligations consist primarily of our convertible debt. In addition, we also have facility mortgages, facility leases, equipment financing arrangements and other obligations. Due to the uncertainty with respect to the timing of future cash flows associated with our unrecognized tax benefits, we are unable to make reasonably reliable estimates of the period of cash settlement with the respective taxing authorities. Therefore, we have excluded $78 million of gross unrecognized tax benefits from our contractual obligations table above.

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 percent convertible senior notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes. As a result, the principal balance of the 2¾ percent notes following the repurchase in November 2014 was $61.2 million.

In December 2016, we issued an additional $185.5 million of 1 percent convertible senior notes in exchange for the redemption of $61.1 million of our 2¾ percent convertible senior notes. At December 31, 2017, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At December 31, 2017, we had the following 1 percent convertible senior notes outstanding (amounts in millions except price per share data):

	1 Percent Convertible Senior Notes
Outstanding principal balance	$ 685.5
Original issue date ($500 million of principal)	November 2014
Additional issue date ($185.5 million of principal)	December 2016
Maturity date	November 2021
Interest rate	1 percent
Conversion price per share	$ 66.81
Total shares of common stock subject to conversion	10.3

Interest is payable semi-annually for the 1 percent notes. The notes are convertible under certain conditions, at the option of the note holders. We 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 percent notes prior to maturity, and no sinking fund is provided for them. Holders of the 1 percent 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 percent notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus accrued and unpaid interest.

Financing Arrangements

In June 2015, we entered into a five-year revolving line of credit agreement with Morgan Stanley Private Bank, National Association, or Morgan Stanley. We amended the credit agreement in February 2016 to increase the amount available for us to borrow. Under the amended credit agreement, Morgan Stanley will provide a maximum of $30 million of revolving credit for general working capital purposes. Any loans under the credit agreement have interest payable monthly in arrears at a borrowing rate based on our option of:

(i) a floating rate equal to the one-month London Interbank Offered Rate, or LIBOR, in effect plus 1.25 percent per annum;
(ii) a fixed rate equal to LIBOR plus 1.25 percent for a period of one, two, three, four, six, or twelve months as elected by us; or
(iii) a fixed rate equal to the LIBOR swap rate during the period of the loan.

Additionally, we pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility. As of December 31, 2017, we had $12.5 million in outstanding borrowings under the credit facility with a 2.31 percent fixed interest rate and a maturity date of September 2019, which we used to fund our capital equipment needs consistent with our historical practice to finance these costs.

The credit agreement includes customary affirmative and negative covenants and restrictions. We are in compliance with all covenants of the credit 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. As a result of the purchase, we extinguished the financing liability we had previously recorded on our balance sheet. The difference between the purchase price of the facility and the carrying value of our financing liability at the time of the purchase was $7.7 million. We recognized this amount as a loss on extinguishment of financing liability for leased facility in our consolidated results of operations in the third quarter of 2017.

We purchased our manufacturing facility in July 2017 for $14.0 million. We previously accounted for the lease on this facility as an operating lease. We capitalized the purchase price of the building as a fixed asset in the third quarter of 2017.

We financed the purchase of our primary R&D facility and manufacturing facility, with mortgage debt of $51.3 million and $9.1 million, respectively. 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, 2017 for the purchase of services, capital equipment and materials as part of our normal course of business.

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

Off-Balance Sheet Arrangements

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

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

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

Item 8. Financial Statements and Supplementary Data

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

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

None.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

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

As of the end of the period covered by this report on Form 10-K, we carried out an evaluation of our disclosure controls and procedures under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of December 31, 2017.

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 United States generally accepted accounting principles.

As of December 31, 2017, 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, 2017.

Attestation Report of the Registered Public Accounting Firm

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2017, 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

The Board of Directors and Stockholders 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, 2017, 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, 2017, 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 Ionis Pharmaceuticals, Inc. as of December 31, 2017 and 2016, and the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2017, and the related notes and our report dated February 28, 2018 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 28, 2018

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, 2017 (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.

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 "Section 16(a) Beneficial Ownership Reporting Compliance" contained in the Proxy Statement.

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

Item 11. Executive Compensation

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

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

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

Securities Authorized for Issuance under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2017.

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)	9,396,796	$ 44.52	8,158,366	(b)
Total	9,396,796	$ 44.52	8,158,366	

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

(b) Of these shares, 668,232 remained available for purchase under the ESPP as of December 31, 2017. The ESPP incorporates an evergreen formula pursuant to which on January 1 of each year, we automatically increase the aggregate number of shares reserved for issuance under the plan by 150,000 shares.

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

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

Item 14. Principal Accounting Fees and Services

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

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Index to Financial Statements

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

(a)(2) Index to Financial Statement Schedules

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

(a)(3) Index to Exhibits

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991.
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 dated filed December 13, 2000 and incorporated herein by reference.
4.2	Specimen Common Stock Certificate.
4.3	Indenture, dated as of August 13, 2012, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 2¾ percent Convertible Senior Note due 2019. - Filed as an exhibit to the Registrant's Report on Form 8-K filed August 13, 2012 and incorporated herein by reference.
4.4	Indenture, dated as of November 17, 2014, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 1.00 percent Convertible Senior Note due 2021. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed November 21, 2014 and incorporated herein by reference.
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 Notice of Annual Meeting and Proxy Statement for the 2009 Annual Meeting of Stockholders, filed with the SEC on April 20, 2009, and incorporated herein by reference.
10.4	Form of Employee Confidential Information and Inventions Agreement.
10.5	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1998 and incorporated herein by reference.
10.6	Collaboration and License Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - Filed as an exhibit to the Registrant's report on Form 10-Q as amended for the quarter ended June 30, 2001 and incorporated herein by reference.
10.7	Amendment #1 to the Research, Development and License Agreement dated May 11, 2011 by and between the Registrant and Glaxo Group Limited. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.8	Amended and Restated Collaboration and License Agreement between the Registrant and Antisense Therapeutics Ltd dated February 8, 2008. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.9	Amended and Restated License Agreement between the Registrant and Atlantic Pharmaceuticals Limited dated November 30, 2009. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - Filed as an exhibit to the Registrant's Annual Report as Form 10-K for the year ended December 31, 2009 and incorporated herein by reference.

10.10	Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen MA Inc. dated October 20, 2017. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.11	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.
10.12	Amendment #1 between the Registrant and Bayer AG dated February 10, 2017. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.13	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.
10.14*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended. - Filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement, for the 2014 Annual Meeting of Stockholders, filed with the SEC on April 25, 2014, and incorporated herein by reference.
10.15*	Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan. - Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012 and incorporated herein by reference.
10.16*	Amended and Restated Severance Agreement dated December 3, 2008 between the Registrant and Stanley T. Crooke. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 5, 2008 and incorporated herein by reference.
10.17	Research Collaboration, Option and License Agreement between the Registrant and Biogen MA Inc. dated December 19, 2017. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.18*	Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan - Filed as an exhibit to the Registrant's Notice of 2011 Annual Meeting of Stockholders and Proxy Statement filed with the SEC on April 28, 2011, and incorporated herein by reference.
10.19*	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.
10.20*	Form of 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.
10.21	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.
10.22*	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.
10.23*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan. - Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2004 and incorporated herein by reference.
10.24	Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated March 30, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.25	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.
10.26	Research Agreement dated August 10, 2011 between the Registrant and CHDI Foundation, Inc. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.27	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.

10.28	Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated January 3, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.29	DMPK Research, Development, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated June 27, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012 and incorporated herein by reference.
10.30	Amendment #2 to Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated October 30, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.31	Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated December 7, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.32	Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated December 10, 2012. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.33	HTT Research, Development, Option and License Agreement among the Registrant, F. Hoffmann-La Roche Ltd and Hoffman-La Roche Inc. dated April 8, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.34	Letter Agreement between the Registrant and CHDI Foundation, Inc. dated April 8, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.35	Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated September 5, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.36	Amendment #1 to Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated August 13, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.37	Letter Agreement Amendment between the Registrant and Biogen Idec International Holding Ltd dated January 27, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.38	Amendment No. 3 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated July 10, 2013. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.39	Amendment #4 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated April 10, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.40	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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.41	Exclusive License Agreement between the Registrant and the University of Massachusetts dated January 14, 2010. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.

10.42	Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated October 26, 2011. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.43	Amendment to Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated March 14, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.44	Amendment #1 to the Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated December 15, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.45	Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 22, 2014. Portions of this exhibit have been omitted and separately filed with the SEC. - 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.
10.46	Amendment No.2 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated October 15, 2014. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment. - 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.
10.47	Strategic Collaboration Agreement between the Registrant and AstraZeneca AB dated July 31, 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 September 30, 2015 and incorporated herein by reference.
10.48	Amendment #6 to Research, Development and License Agreement between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated September 2, 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 September 30, 2015 and incorporated herein by reference.
10.49	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. 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 September 30, 2015 and incorporated herein by reference.
10.50	License Agreement between the Registrant and Bayer Pharma AG dated May 1, 2015. Portions of this exhibit have been omitted and separately filed with the SEC. - Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2015 and incorporated herein by reference.
10.51	Line of Credit Agreement between the Registrant and Morgan Stanley Private Bank, National Association dated June 16, 2015. - Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2015 and incorporated herein by reference.
10.52	Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated January 8, 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 March 31, 2015 and incorporated herein by reference.
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. 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 March 31, 2015 and incorporated herein by reference.
10.54	Amendment No.1 to Loan Documents between the Registrant and Morgan Stanley Private Bank, National Association dated December 30, 2015. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed January 5, 2016 and incorporated herein by reference.
10.55	Amendment No.2 to Line of Credit Agreement between the Registrant and Morgan Stanley Private Bank, National Association dated February 24, 2016. Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2015 and incorporated herein by reference.
10.56	Amendment No.3 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated January 18, 2016. 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 March 31, 2016 and incorporated herein by reference.

10.57	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. 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 March 31, 2016 and incorporated herein by reference.
10.58	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 and separately filed with the SEC.
10.59	Letter Agreement between the Registrant and Biogen MA Inc. dated October 28, 2016. Portions of this exhibit have been omitted and separately filed with the SEC. Portions of this exhibit have been omitted and separately filed with the SEC.
10.60	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.
10.61	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.
10.62	Environmental Indemnity Agreement among the Registrant, Ionis Faraday, LLC and UBS AG dated July 18, 2017. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.63*	Amendment to Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan. - Filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement, for the 2017 Annual Meeting of Stockholders, filed with the SEC on April 10, 2017, and incorporated herein by reference.
14.1	Registrant's Code of Ethics and Business Conduct.
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, 2016, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of stockholders' equity, (iv) consolidated statements of cash flows, and (v) notes to consolidated financial statements (detail tagged).

* 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 28th day of February, 2018.

IONIS PHARMACEUTICALS, INC.

By: /s/ STANLEY T. CROOKE
Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board, President and 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 Stanley T. Crooke 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/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	February 28, 2018
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	February 28, 2018
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director and Senior Strategic Advisor	February 28, 2018
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 28, 2018
/s/ BREAUX CASTLEMAN Breaux Castleman	Director	February 28, 2018
/s/ JOSEPH KLEIN Joseph Klein, III	Director	February 28, 2018
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Director	February 28, 2018
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	February 28, 2018
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	February 28, 2018

IONIS PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders 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, 2017 and 2016, and the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2017, 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, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, 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, 2017, 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 28, 2018 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 these 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 included 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.

/s/ ERNST & YOUNG LLP

We have served as the Company's auditor since 1989

San Diego, California
February 28, 2018

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

	December 31,	
	2017	**2016**
ASSETS		
Current assets:		
Cash and cash equivalents	$ 129,630	$ 84,685
Short-term investments	893,085	580,538
Contracts receivable	62,955	108,043
Inventories	9,982	7,489
Other current assets	72,332	17,177
Total current assets	1,167,984	797,932
Property, plant and equipment, net	121,907	92,845
Patents, net	22,004	20,365
Deposits and other assets	10,129	1,325
Total assets	$ 1,322,024	$ 912,467
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 24,886	$ 21,120
Accrued compensation	25,151	24,186
Accrued liabilities	66,618	36,013
Current portion of long-term obligations	1,621	1,185
Current portion of deferred contract revenue	106,465	51,280
Total current liabilities	224,741	133,784
Long-term deferred contract revenue	72,708	91,198
1 percent convertible senior notes	533,111	500,511
Long-term obligations, less current portion	12,974	15,050
Long-term financing liability for leased facility	—	72,359
Long-term mortgage debt	59,771	—
Total liabilities	903,305	812,902
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 124,976,373 and 121,636,273 shares issued and outstanding at December 31, 2017 and December 31, 2016, respectively	125	122
Additional paid-in capital	1,549,904	1,311,229
Accumulated other comprehensive income (loss)	(31,759)	(30,358)
Accumulated deficit	(1,187,398)	(1,181,428)
Total Ionis stockholders' equity	330,872	99,565
Noncontrolling interest in Akcea Therapeutics, Inc.	87,847	—
Total stockholders' equity	418,719	99,565
Total liabilities and stockholders' equity	$ 1,322,024	$ 912,467

See accompanying notes.

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

	Years Ended December 31,		
	2017	**2016**	**2015**
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 112,540	$ 883	$ —
Licensing and other royalty revenue	9,519	19,839	2,343
Total commercial revenue	122,059	20,722	2,343
Research and development revenue under collaborative agreements	385,607	325,898	281,360
Total revenue	507,666	346,620	283,703
Expenses:			
Research, development and patent	374,644	344,320	322,292
Selling, general and administrative	108,488	48,616	37,173
Total operating expenses	483,132	392,936	359,465
Income (loss) from operations	24,534	(46,316)	(75,762)
Other income (expense):			
Investment income	7,805	5,472	4,377
Interest expense	(44,752)	(38,795)	(36,732)
Gain on investment in Regulus Therapeutics Inc.	374	—	20,211
Loss on extinguishment of financing liability for leased facility	(7,689)	—	—
Loss on early retirement of debt	—	(3,983)	—
Other expenses	(3,548)	—	—
Loss before income tax benefit (expense)	(23,276)	(83,622)	(87,906)
Income tax benefit (expense)	5,980	(2,934)	(372)
Net loss	(17,296)	(86,556)	(88,278)
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	11,326	—	—
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (5,970)	$ (86,556)	$ (88,278)
Basic net income (loss) per share	$ 0.08	$ (0.72)	$ (0.74)
Shares used in computing basic net income (loss) per share	124,016	120,933	119,719
Diluted net income (loss) per share	$ 0.08	$ (0.72)	$ (0.74)
Shares used in computing diluted net income (loss) per share	126,098	120,933	119,719

See accompanying notes.

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

	Years Ended December 31,		
	2017	**2016**	**2015**
Net loss	$ (17,296)	$ (86,556)	$ (88,278)
Unrealized losses on investments, net of tax	(960)	(17,219)	(33,101)
Reclassification adjustment for realized (gains) losses included in net loss	(374)	447	(20,211)
Currency translation adjustment	(67)	(21)	—
Comprehensive loss	(18,697)	(103,349)	(141,590)
Comprehensive loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	11,421	—	—
Comprehensive loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (7,276)	$ (103,349)	$ (141,590)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2017, 2016 and 2015
(In thousands)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at December 31, 2014	118,443	$ 118	$ 1,224,509	$ 39,747	$ (1,006,594)	$ 257,780	$ —	$ 257,780
Net loss	—	—	—	—	(88,278)	(88,278)	—	(88,278)
Change in unrealized gains (losses), net of tax	—	—	—	(53,312)	—	(53,312)	—	(53,312)
Issuance of common stock in connection with employee stock plans	1,908	2	24,888	—	—	24,890	—	24,890
Stock-based compensation expense	—	—	59,314	—	—	59,314	—	59,314
Excess tax benefits from stock-based compensation awards	—	—	396	—	—	396	—	396
Balance at December 31, 2015	120,351	$ 120	$ 1,309,107	$ (13,565)	$ (1,094,872)	$ 200,790	$ —	$ 200,790
Net loss	—	—	—	—	(86,556)	(86,556)	—	(86,556)
Change in unrealized gains (losses), net of tax	—	—	—	(16,772)	—	(16,772)	—	(16,772)
Foreign currency translation	—	—	—	(21)	—	(21)	—	(21)
Issuance of common stock in connection with employee stock plans	1,285	2	13,706	—	—	13,708	—	13,708
2¾ percent convertible senior notes redemption, equity portion	—	—	(128,888)	—	—	(128,888)	—	(128,888)
1 percent convertible senior notes, equity portion, net of issuance costs	—	—	43,335	—	—	43,335	—	43,335
Stock-based compensation expense	—	—	72,108	—	—	72,108	—	72,108
Excess tax benefits from stock-based compensation awards	—	—	1,861	—	—	1,861	—	1,861
Balance at December 31, 2016	121,636	$ 122	$ 1,311,229	$ (30,358)	$ (1,181,428)	$ 99,565	$ —	$ 99,565
Net loss	—	—	—	—	(5,970)	(5,970)	—	(5,970)
Change in unrealized gains (losses), net of tax	—	—	—	(1,334)	—	(1,334)	—	(1,334)
Foreign currency translation	—	—	—	(67)	—	(67)	—	(67)
Novartis stock purchase	1,631	2	71,737	—	—	71,739	—	71,739
Issuance of common stock in connection with employee stock plans	1,709	1	22,931	—	—	22,932	—	22,932
Stock-based compensation expense	—	—	85,975	—	—	85,975	—	85,975
Issuance of Akcea Therapeutics, Inc. common stock in conjunction with initial public offering	—	—	157,270	—	—	157,270	—	157,270
Noncontrolling interest in Akcea Therapeutics, Inc. in conjunction with initial public offering	—	—	(90,351)	—	—	(90,351)	90,381	30
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(8,887)	—	—	(8,887)	(2,534)	(11,421)
Balance at December 31, 2017	124,976	$ 125	$ 1,549,904	$ (31,759)	$ (1,187,398)	$ 330,872	$ 87,847	$ 418,719

See accompanying notes.

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

	Years Ended December 31,		
	2017	**2016**	**2015**
Operating activities:			
Net loss	$ (17,296)	$ (86,556)	$ (88,278)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation	6,708	7,481	6,984
Amortization of patents	1,641	1,552	1,381
Amortization of licenses	—	—	1,873
Amortization of premium on investments, net	6,752	6,813	7,812
Amortization of debt issuance costs	1,616	1,225	1,133
Amortization of convertible senior notes discount	30,920	23,890	22,075
Amortization of long-term financing liability for leased facility	3,659	6,693	6,665
Stock-based compensation expense	85,975	72,108	59,314
Gain on investment in Regulus Therapeutics Inc.	(374)	—	(20,211)
Loss on extinguishment of financing liability for leased facility	7,689	—	—
Loss on early retirement of debt	—	3,983	—
Non-cash losses related to patents, licensing, property, plant and equipment and strategic investments	3,302	2,297	1,881
Changes in operating assets and liabilities:			
Contracts receivable	45,088	(96,687)	(7,453)
Inventories	(2,493)	(590)	(609)
Other current and long-term assets	(58,367)	1,603	(4,394)
Long-term income tax receivable	(9,114)	—	—
Accounts payable	1,784	(10,677)	9,211
Income taxes	435	1,069	—
Accrued compensation	965	8,121	3,763
Accrued liabilities and deferred rent	28,564	4,720	(2,140)
Deferred contract revenue	36,695	(59,150)	22,118
Net cash provided by (used in) operating activities	174,149	(112,105)	21,125
Investing activities:			
Purchases of short-term investments	(877,810)	(300,912)	(493,467)
Proceeds from the sale of short-term investments	557,369	364,572	419,584
Purchases of property, plant and equipment	(34,764)	(7,107)	(7,692)
Acquisition of licenses and other assets, net	(3,093)	(4,421)	(4,056)
Purchase of strategic investments	(2,500)	—	—
Proceeds from the sale of Regulus Therapeutics, Inc.	2,507	4,467	25,527
Proceeds from the sale of strategic investments	—	—	52
Net cash (used in) provided by investing activities	(358,291)	56,599	(60,052)
Financing activities:			
Proceeds from equity, net	22,931	13,417	24,888
Proceeds from issuance of common stock in Akcea Therapeutics, Inc. from its initial public offering, net of underwriters' discount	110,438	—	—
Proceeds from building mortgage debt, net of issuance costs	59,750	—	—
Proceeds from the issuance of common stock to Novartis	71,737	—	—
Proceeds from borrowing on line of credit facility	—	4,000	8,500
Proceeds from the sale of Akcea Therapeutics, Inc. common stock to Novartis in a private placement	50,000	—	—
Offering costs paid	(2,037)	(818)	—
Payment to settle financing liability for leased facility	(80,133)	—	—
Excess tax benefits from stock-based compensation awards	—	1,861	396
Principal payments on debt and capital lease obligations	(3,599)	(7,066)	(9,058)
Net cash provided by financing activities	229,087	11,394	24,726
Net increase (decrease) in cash and cash equivalents	44,945	(44,112)	(14,201)
Cash and cash equivalents at beginning of year	84,685	128,797	142,998
Cash and cash equivalents at end of year	$ 129,630	$ 84,685	$ 128,797

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

Supplemental disclosures of cash flow information:	2017	2016	2015
Interest paid	$ 8,035	$ 7,313	$ 6,800
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 1,983	$ 3,439	$ 1,162
1 percent convertible senior notes principal issued related to our December 2016 debt exchange	$ —	$ 185,450	$ —
2¾ percent convertible senior notes principal extinguished related to our December 2016 debt exchange	$ —	$ 61,099	$ —
Unpaid deferred offering costs	$ —	$ 291	$ —

See accompanying notes.

1. Organization and Significant Accounting Policies

Basis of Presentation

In our consolidated financial statements we included the accounts of Ionis Pharmaceuticals, Inc. ("we", "us" or "our") and the consolidated results of our majority-owned affiliate, Akcea Therapeutics, Inc., which we formed in December 2014. In July 2017, Akcea completed an initial public offering, or IPO, and therefore beginning in July 2017, we no longer own 100 percent of Akcea. As of July 19, 2017, the closing of the IPO, we owned approximately 68 percent of Akcea. Refer to the noncontrolling interest in Akcea section in this note for further information related to our accounting for our investment in Akcea.

Organization and Business Activity

We incorporated in California on January 10, 1989. In conjunction with our IPO, we reorganized as a Delaware corporation in April 1991. We were organized principally to develop human therapeutic drugs 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

We compute basic net income (loss) per share by dividing the 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 2017 considered our net income for Ionis on a stand-alone basis plus our share of Akcea's net loss. 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 year. Prior to Akcea's IPO, we owned Akcea Series A convertible preferred stock, which included a six percent cumulative dividend. Upon completion of Akcea's IPO in July 2017, our preferred stock was converted into common stock on a 1:1 basis. The preferred stock dividend was not paid at the IPO because it was not a liquidation event or a change in control. For 2017, Akcea used a two-class method to compute its net income (loss) per share because it had both common and preferred shares outstanding during the year. The two-class method required Akcea to calculate its net income (loss) per share for each class of stock by dividing total distributable losses applicable to preferred and common stock, including the six percent cumulative dividend contractually due to Series A convertible preferred shareholders, by the weighted average of preferred and common shares outstanding during the requisite period. Since Akcea used the two-class method, accounting rules required us to include our portion of Akcea's net income (loss) per share for both Akcea's common and preferred shares which we owned in our calculation of basic and diluted net income per share for 2017. As a result of this calculation, our total net income available to Ionis common stockholders for the calculation of net income per share is different than net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders in the consolidated statements of operations.

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

Year Ended December 31, 2017	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	20,669	$ (2.82)	$ (58,332)
Preferred shares	15,748	(1.55)	(24,344)
Akcea's net loss attributable to our ownership			$ (82,676)
Ionis' stand-alone net income			92,336
Net income available to Ionis common stockholders			$ 9,661
Weighted average shares outstanding			124,016
Basic net income per share			$ 0.08

For 2017, 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 those periods. Diluted common equivalent shares for 2017 consisted of the following (in thousands except per share amounts):

Year Ended December 31, 2017	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 9,661	124,016	$ 0.08
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,619	
Shares issuable upon restricted stock award issuance	—	459	
Shares issuable related to our ESPP	—	4	
Income available to Ionis common stockholders, plus assumed conversions	$ 9,661	126,098	$ 0.08

For 2017, the calculation excluded the 1 percent and 2¾ percent notes because the effect on diluted earnings per share was anti-dilutive.

As we incurred a net loss for 2016 and 2015, 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:

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

Revenue Recognition

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 often enter into agreements to license and sell our technology on an exclusive or non-exclusive basis in exchange for upfront fees, license fees, milestone payments and/or royalties. We generally recognize as revenue immediately license payments with stand-alone value when the license is delivered and we are reasonably assured of collecting the resulting receivable. We recognize royalty revenue in the period in which the counterparty sells the related product, unless we are unable to obtain information to estimate the royalty. For example, in 2017 we recorded SPINRAZA royalty revenue of $112.5 million.

Research and development revenue under collaborative agreements

Arrangements with multiple deliverables

Our collaboration agreements typically contain multiple elements, or deliverables, including technology licenses or options to obtain technology licenses, research and development services, and in certain cases manufacturing services, and we allocate the consideration to each unit of accounting based on the relative selling price of each deliverable.

Amendments to agreements

From time to time we amend our collaboration agreements. For these agreements, before we identify our deliverables and allocate consideration to each unit of accounting, we must determine if the amendment should be accounted for as a separate agreement, or if the amendment and any undelivered elements for the original agreement should be accounted for as a single new arrangement.

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 active pharmaceutical ingredient, or 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, there was a substantial increase in the consideration we are eligible to receive and a significant change in the deliverables we will provide to Bayer. As a result, we concluded that the amendment should be evaluated with the undelivered elements of the original agreement as a single new arrangement. Therefore, we evaluated our original and 2017 amended agreements with Bayer together to determine our deliverables. We concluded that the 2017 amendment did not impact the items we already delivered to Bayer.

Identifying deliverables and units of accounting

We evaluate the deliverables in our collaboration agreements to determine whether they meet the criteria to be accounted for as separate units of accounting or whether they should be combined with other deliverables and accounted for as a single unit of accounting. When the delivered items in an arrangement have "stand-alone value" to our customer, we account for the deliverables as separate units of accounting. Delivered items have stand-alone value if they are sold separately by any vendor or the customer could resell the delivered items on a stand-alone basis. For example, our 2017 amended agreement with Bayer has multiple elements. We evaluated the deliverables in this arrangement when we entered into the 2017 amended agreement and determined that certain of the deliverables have stand-alone value. Below is a list of the three units of accounting under our 2017 amended agreement:

- The exclusive license we granted to Bayer to develop and commercialize IONIS-FXI-L$_{Rx}$ for the treatment of thrombosis;
- The development services we agreed to perform for IONIS-FXI-L$_{Rx}$ and IONIS-FXI$_{Rx}$; and
- The remaining undelivered IONIS-FXI$_{Rx}$ API that was part of the original agreement.

We determined that each of these three units of accounting have stand-alone value. The license we granted to Bayer has stand-alone value because it gives Bayer the exclusive right to develop IONIS-FXI-L_{Rx} or to sublicense its rights. The development services and the remaining undelivered supply of API each have stand-alone value because Bayer or another third party could provide these items without our assistance.

Measurement and allocation of arrangement consideration

Our collaborations may provide for various types of payments to us including upfront payments, funding of research and development, milestone payments, licensing fees and royalties on product sales. We initially allocate the amount of consideration that is fixed and determinable at the time the agreement is entered into and exclude contingent consideration. We allocate the consideration to each unit of accounting based on the relative selling price of each deliverable. We use the following hierarchy of values to estimate the selling price of each deliverable: (i) vendor-specific objective evidence of fair value; (ii) third-party evidence of selling price; and (iii) best estimate of selling price, or BESP. BESP reflects our best estimate of what the selling price would be if we regularly sold the deliverable on a stand-alone basis. We recognize the revenue allocated to each unit of accounting as we deliver the related goods or services. If we determine that we should treat certain deliverables as a single unit of accounting, then we recognize the revenue ratably over our estimated period of performance.

We determined that the allocable arrangement consideration for the Bayer 2017 amended agreement was $76.3 million, comprised of the $75 million we received as part of the amendment and the remaining amount of the $100 million upfront payment we had not yet recognized into revenue, related to the undelivered API. We allocated the consideration based on the relative BESP of each unit of accounting. We engaged a third party, independent valuation specialist to assist us with determining BESP. We estimated the selling price of the license granted for IONIS-FXI-L_{Rx} by using the relief from royalty method. Under this method, we estimated the amount of income, net of taxes, for IONIS-FXI-L_{Rx}. We then discounted the projected income to present value. The significant inputs we used to determine the projected income of the license included:

- Estimated future product sales;
- Estimated royalties on future product sales;
- Contractual milestone payments;
- Expenses we expect to incur;
- Income taxes; and
- An appropriate discount rate.

We estimated the selling price of the development services by using our internal estimates of the cost to perform the specific services and estimates of expected cash outflows to third parties for services and supplies over the expected period that we will perform the development services. The significant inputs we used to determine the selling price of the development services included:

- The number of internal hours 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 BESP of the services we will perform and the API we will deliver in our 2017 amended Bayer transaction, accounting guidance required us to include a markup for a reasonable profit margin.

Based on the units of accounting under the 2017 amended agreement, we allocated the $76.3 million of allocable consideration as follows:

- $64.9 million to the IONIS-FXI-L_{Rx} exclusive license;
- $11.0 million for development services for IONIS-FXI-L_{Rx} and IONIS-FXI_{Rx}; and
- $0.4 million for the remaining delivery of IONIS-FXI_{Rx} API.

Assuming a constant selling price for the other elements in the arrangement, if there was an assumed 10 percent increase or decrease in the estimated selling price of the IONIS-FXI-L_{Rx} license, we determined that the revenue we would have allocated to the IONIS-FXI-L_{Rx} license would change by approximately one percent, or $0.7 million, from the amount we recorded.

Timing of revenue recognition

We recognize revenue as we deliver each item under the arrangement and the related revenue is realizable and earned. For example, we recognized revenue for the exclusive license we granted Bayer for IONIS-FXI-L_{Rx} in the first quarter of 2017 because that was when we delivered the license. We also recognize revenue over time as we provide services. Our collaborative agreements typically include a research and/or development project plan outlining the activities the agreement requires each party to perform during the collaboration. We estimate our period of performance at the inception of the agreement when the agreements we enter into do not clearly define such information. We then recognize revenue from development services ratably over such period. In certain instances, the period of performance may change as the development plans for our drugs progress. If our estimates and judgments change over the course of our collaboration agreements, it may affect the timing and amount of revenue that we recognize in future periods. We recognize any changes in estimates on a prospective basis.

The following are the periods over which we are recognizing revenue for each of our units of accounting under our 2017 amended Bayer agreement:

- We recognized the portion of the consideration attributed to the IONIS-FXI-L_{Rx} license in the first quarter of 2017 because we delivered the license and earned the revenue;
- We are recognizing the amount attributed to the development services for IONIS-FXI-L_{Rx} and IONIS-FXI_{Rx} over the period of time we are performing the services; and
- We are recognizing the amount attributed to the remaining API supply as we deliver it to Bayer.

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 they should be accounted for individually as distinct arrangements or whether the separate agreements are, in substance, a single multiple element arrangement. We evaluate whether the negotiations are conducted jointly as part of a single negotiation, whether the deliverables are interrelated or interdependent, whether fees in one arrangement are tied to performance in another arrangement, and whether elements in one arrangement are essential to another arrangement. Our evaluation involves significant judgment to determine whether a group of agreements might be so closely related that they are, in effect, part of a single arrangement. For example, in the first quarter of 2017, we and Akcea entered into two separate agreements with Novartis at the same time: a collaboration agreement and a stock purchase agreement, or SPA.

Akcea entered into a collaboration agreement with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the collaboration agreement, Akcea received a $75 million upfront payment. For each drug, Akcea is responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the Food and Drug Administration, or FDA, and delivering API. Under the collaboration agreement, Novartis has an exclusive option to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. If Novartis exercises an option for one of these drugs, Novartis will pay Akcea a $150 million license fee and will assume all further global development, regulatory and commercialization activities and costs for the licensed drug. Akcea is also eligible to receive a development milestone payment, milestone payments if Novartis achieves pre-specified regulatory milestones, commercial milestones and tiered royalties on net sales from each drug under the collaboration.

Under the SPA, Novartis purchased 1.6 million shares of Ionis' common stock for $100 million in the first quarter of 2017 and paid a premium over the weighted average trading price at the time of purchase. Additionally, the SPA required Novartis to purchase $50 million of Akcea's common stock in a concurrent private placement with Akcea's IPO in July 2017.

We evaluated the Novartis agreements to determine whether we should treat the agreements separately or as a single arrangement. We considered that the agreements were negotiated concurrently and in contemplation of one another. Additionally, the same individuals were involved in the negotiations of both agreements. Based on these facts and circumstances, we concluded that we should treat both agreements as a single arrangement and evaluate the provisions of the agreements on a combined basis. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements* for further discussion of the accounting treatment for the Novartis collaboration.

Milestone payments

Our collaborations often include contractual milestones, which typically relate to the achievement of pre-specified development, regulatory and/ or commercialization events. These three categories of milestone events reflect the three stages of the life-cycle of our drugs, which we describe in more detail in the following paragraphs.

Prior to the first stage in the life-cycle of our drugs, we perform a significant amount of work using our proprietary antisense technology to design chemical compounds that interact with specific genes that are good targets for drug discovery. From these research efforts, we hope to identify a development candidate. The designation of a development candidate is the start of the development stage, which is the first stage in the life-cycle of our drugs. A development candidate is a chemical compound that has demonstrated the necessary safety and efficacy in preclinical animal studies to warrant further study in humans.

During the first step of the development stage, we or our partners study our drugs in Investigational New Drug, or IND,-enabling studies, which are animal studies intended to support an IND application and/or the foreign equivalent. An approved IND allows us or our partners to study our development candidate in humans. If the regulatory agency approves the IND, we or our partners initiate a Phase 1 clinical trial in which we typically enroll a small number of healthy volunteers to ensure the development candidate is safe for use in patients. If we or our partners determine that a development candidate is safe based on the Phase 1 data, we or our partners initiate Phase 2 studies that are generally larger studies in patients with the primary intent of determining the preliminary efficacy and safety of the development candidate.

The final step in the development stage is Phase 3 studies to gather the necessary safety and efficacy data to request marketing authorization from the FDA and/or foreign equivalents. Phase 3 studies typically involve larger numbers of patients and can take up to several years to complete.

If the data gathered during the Phase 3 trials demonstrates acceptable safety and efficacy results, we or our partner will submit an application to the FDA and/or its foreign equivalents for marketing authorization. This stage of the drug's life-cycle is the regulatory stage.

If the FDA or a foreign equivalent grants marketing authorization for a drug, it moves into the commercialization stage. During this stage we or our partner will market and sell the drug to patients. Although our partner may ultimately be responsible for marketing and selling a partnered drug, our efforts to discover and develop a drug that is safe, effective and reliable contributes significantly to our partner's ability to successfully sell the drug. The FDA and its foreign equivalents have the authority to impose significant restrictions on an approved drug through the product label and on advertising, promotional and distribution activities. Therefore, our efforts designing and executing the necessary animal and human studies are critical to obtaining claims in the product label from the regulatory agencies that would allow us or our partner to successfully commercialize our drug. Further, the patent protection afforded our drugs as a result of our initial patent applications and related prosecution activities in the United States and foreign jurisdictions are critical to our partner's ability to sell our drugs without competition from generic drugs. The potential sales volume of an approved drug is dependent on several factors including the size of the patient population, market penetration of the drug, and the price charged for the drug.

Generally, the milestone events contained in our partnership agreements coincide with the progression of our drugs from development, to marketing authorization and then to commercialization. The process of successfully discovering a new development candidate, having it approved and ultimately selling it for a profit is highly uncertain. As such, the milestone payments we may earn from our partners involve a significant degree of risk to achieve. Therefore, as a drug progresses through the stages of its life-cycle, the value of the drug generally increases.

Development milestones in our partnerships may include the following types of events:

- Designation of a development candidate. Following the designation of a development candidate, IND-enabling animal studies for a new development candidate generally take 12 to 18 months to complete.
- Initiation of a Phase 1 clinical trial. Generally, Phase 1 clinical trials take one to two years to complete.
- Initiation or completion of a Phase 2 clinical trial. Generally, Phase 2 clinical trials take one to three years to complete.
- Initiation or completion of a Phase 3 clinical trial. Generally, Phase 3 clinical trials take two to four years to complete.

Regulatory milestones in our partnerships may include the following types of events:

- Filing of regulatory applications for marketing authorization such as a New Drug Application, or NDA, in the United States or a Marketing Authorization Application, or MAA, in Europe. Generally, it takes six to twelve months to prepare and submit regulatory filings.
- Obtaining marketing authorization in a major market, such as the United States, Europe or Japan. Generally it takes one to two years after an application is submitted to obtain authorization from the applicable regulatory agency.

Commercialization milestones in our partnerships may include the following types of events:

- First commercial sale in a particular market, such as in the United States or Europe.
- Product sales in excess of a pre-specified threshold, such as annual sales exceeding $1 billion. The amount of time to achieve this type of milestone depends on several factors including but not limited to the dollar amount of the threshold, the pricing of the product and the pace at which customers begin using the product.

We assess whether a substantive milestone exists at the inception of our agreements. When a substantive milestone is achieved, we recognize revenue related to the milestone payment immediately. For our licensing and collaboration agreements in which we are involved in the discovery and/or development of the related drug or provide the partner with access to new technologies we discover, we have determined that the majority of future development, regulatory and commercialization milestones are substantive. For example, we consider most of the milestones associated with our strategic alliance with Biogen substantive because we are using our antisense drug discovery platform to discover and develop new drugs against targets for neurological diseases. In evaluating if a milestone is substantive we consider whether:

- Substantive uncertainty exists as to the achievement of the milestone event at the inception of the arrangement;
- The achievement of the milestone involves substantive effort and can only be achieved based in whole or in part on our performance or the occurrence of a specific outcome resulting from our performance;
- The amount of the milestone payment appears reasonable either in relation to the effort expended or to the enhancement of the value of the delivered items;
- There is no future performance required to earn the milestone; and
- The consideration is reasonable relative to all deliverables and payment terms in the arrangement.

If any of these conditions are not met, we do not consider the milestone to be substantive and we defer recognition of the milestone payment and recognize it as revenue over our estimated period of performance, if any. Further information about our collaborative arrangements can be found in Note 6, *Collaborative Arrangements and Licensing Agreements*.

Option to license

In several of our collaboration agreements, we provide our partner with an option to obtain a license to one or more of our drugs. When we have a multiple element arrangement that includes an option to obtain a license, we evaluate if the option is a deliverable at the inception of the arrangement. We do not consider the option to be a deliverable if we conclude that it is substantive and not priced at a significant and incremental discount. We consider an option substantive if, at the inception of the arrangement, we are at risk as to whether our collaboration partner will choose to exercise its option to obtain the license. In those circumstances, we do not include the associated license fee in the allocable consideration at the inception of the agreement. Rather, we account for the license fee when our partner exercises its option. For example, during 2017, we earned license fee revenue when three of our partners, Bayer, Janssen and Roche, exercised their options to license three of our drugs, which under the respective agreements we concluded to be substantive options at inception. As a result, in 2017 we recognized the related revenue immediately in research and development revenue under collaborative agreements on our statement of operations as these amounts relate to drugs in development under research and development collaboration arrangements.

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, 2017, 2016 and 2015, research and development expenses were $372.5 million, $340.4 million and $319.5 million, respectively. A portion of the costs included in research and development expenses are costs associated with our partner agreements. For the years ended December 31, 2017, 2016 and 2015, research and development costs of approximately $59.5 million, $187.1 million and $161.7 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 United States Patent and Trademark Office, or foreign equivalent, issues the patent. The weighted average remaining amortizable life of our issued patents was 10.1 years at December 31, 2017.

The cost of our patents capitalized on our consolidated balance sheet at December 31, 2017 and 2016 was $30.8 million and $28.8 million, respectively. Accumulated amortization related to patents was $8.8 million and $8.4 million at December 31, 2017 and 2016, respectively.

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

Years Ending December 31,	Amortization (in millions)
2018	$ 1.6
2019	$ 1.4
2020	$ 1.3
2021	$ 1.3
2022	$ 1.2

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 2017, 2016 and 2015, patent expenses were $2.1 million, $3.9 million and $2.8 million, respectively, and included non-cash charges related to the write-down of our patent costs to their estimated net realizable values of $0.4 million, $2.3 million and $1.1 million, respectively.

Accrued Liabilities

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

	December 31,	
	2017	2016
Clinical expenses	$ 16,347	$ 23,428
In-licensing expenses	33,790	6,430
Other miscellaneous expenses	16,481	6,155
Total accrued liabilities	$ 66,618	$ 36,013

Noncontrolling Interest in Akcea Therapeutics, Inc.

In July 2017, Akcea completed an IPO. Akcea raised $193.8 million of aggregate gross proceeds from the IPO, including $50.0 million from a private placement by Novartis. Akcea's net proceeds were $182.4 million. As part of Akcea's IPO, we invested $25.0 million. In conjunction with the IPO, the shares of Akcea's series A convertible preferred stock we owned converted into shares of Akcea's common stock. Additionally, the amount outstanding under Akcea's line of credit with us converted into shares of Akcea's common stock.

Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea's stock and consolidated 100 percent of Akcea's results in our financial statements. In connection with Akcea's IPO, shares of Akcea's common stock were sold to third parties. We owned approximately 68 percent of Akcea after the IPO and at December 31, 2017. The shares third parties own represent an interest in Akcea's equity that is not controlled by us. However, as we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our consolidated financial statements. The noncontrolling interest attributable to other owners of Akcea's common stock is reflected in a separate line on the statement of operations and a separate line within stockholders' equity in our consolidated financial statements. In addition, we recorded a noncontrolling interest adjustment to account for the stock options that Akcea grants for its common stock, which if exercised, will dilute our ownership in Akcea. This adjustment was reflected as 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 from inception through the IPO. Going forward, each period we will reclassify Akcea's stock-based compensation expense in a similar fashion.

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 Short-Term 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 investments as "available-for-sale" and carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments. We use the specific identification method to determine the cost of securities sold.

We have equity investments of less than 20 percent in privately and publicly held biotechnology companies that we received as part of a technology license or partner agreement. At December 31, 2017, we held equity investments in one publicly held company, Antisense Therapeutics Limited, or ATL. Furthermore, we held cost method investments in five companies, Atlantic Pharmaceuticals Limited, Dynacure SAS, Kastle Therapeutics, Seventh Sense Biosystems and Suzhou Ribo Life Science Co., Ltd.

We account for our equity investments in publicly held companies at fair value and record unrealized gains and losses related to temporary increases and decreases in the stock as a separate component of comprehensive income (loss). We account for our equity investments in privately held companies under the cost method of accounting because we own less than 20 percent and do not have significant influence over their operations. Realization of our equity position in these private companies is usually uncertain. When realization of our investment is uncertain, we record a full valuation allowance. In determining if and when a decrease in market value below our cost in our equity positions is temporary or other-than-temporary, we examine historical trends in the stock price, the financial condition of the company, near term prospects of the company and our current need for cash. If we determine that a decline in value in either a public or private investment is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs.

Inventory Valuation

We capitalize the costs of raw materials that we purchase for use in producing our drugs because until we use these raw materials they have alternative future uses. We include in inventory raw material costs for drugs 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 drug. For example, if one of our drugs failed, we could use the raw materials for that drug to manufacture our other drugs. We expense these costs when we begin to manufacture API for a particular drug. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method, or FIFO. We review inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf life of raw materials, alternative uses for our drugs and clinical trial materials, and historical write-offs. We did not record any inventory write-offs for the years ended December 31, 2017, 2016 or 2015. Total inventory was $10.0 million and $7.5 million as of December 31, 2017 and 2016, respectively.

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, 2017	December 31, 2016
Computer software, laboratory, manufacturing and other equipment	3 to 10	$ 66,558	$ 63,287
Building, building improvements and building systems	15 to 40	92,770	48,909
Land improvements	20	2,853	2,853
Leasehold improvements	5 to 15	26,748	41,736
Furniture and fixtures	5 to 10	6,161	5,937
		195,090	162,722
Less accumulated depreciation		(87,676)	(80,075)
		107,414	82,647
Land		14,493	10,198
Total		$ 121,907	$ 92,845

We depreciate our leasehold improvements using the shorter of the estimated useful life or remaining lease term. As a result of the purchase of our primary manufacturing facility in 2017, we reclassed previously capitalized leasehold improvements to building, building improvements and building systems. Additionally, during 2017 we made additional improvements and expansions of our buildings to accommodate the growth in our business.

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.

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 $0.8 million, $2.3 million and $1.9 million for the years ended December 31, 2017, 2016 and 2015, respectively, related primarily to the write-down of intangible assets.

Use of Estimates

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

Stock-Based Compensation Expense

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

We use the Black-Scholes model as our method of valuing option awards and stock purchase rights under our ESPP. On the grant date, we use our stock price and assumptions regarding a number of highly complex and subjective 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. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because our employee stock options have certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of our employee stock options. Although we determine the estimated fair value of employee stock options using an option-pricing model, that value may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

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

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

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

Accumulated other comprehensive income (loss)

Accumulated other comprehensive income (loss) is primarily comprised of unrealized gains and losses on investments, net of taxes and adjustments we made to reclassify realized gains and losses on investments from other accumulated comprehensive income (loss) to our Consolidated Statement of Operations. The following table summarizes changes in accumulated other comprehensive income (loss) for the years ended December 31, 2017, 2016 and 2015 (in thousands):

	Years Ended December 31,		
	2017	2016	2015
Beginning balance accumulated other comprehensive (loss) income	$ (30,358)	$ (13,565)	$ 39,747
Unrealized losses on securities, net of tax (1)	(960)	(17,219)	(33,101)
Amounts reclassified from accumulated other comprehensive (loss) income (2)	(374)	447	(20,211)
Currency translation adjustment	(67)	(21)	—
Net other comprehensive loss for the period	(1,401)	(16,793)	(53,312)
Ending balance accumulated other comprehensive loss	$ (31,759)	$ (30,358)	$ (13,565)

(1) There was no tax expense for other comprehensive loss for the years ended December 31, 2017, 2016 or 2015.

(2) Amounts for 2015 and 2017 are included in the separate line called "Gain on investment in Regulus Therapeutics Inc." on our Consolidated Statement of Operations.

Convertible Debt

We account for convertible debt instruments, including our 1 percent and 2¾ percent 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. We determine the carrying amount of the liability component by measuring the fair value of similar debt instruments that do not have the conversion feature. If no similar debt instrument exists, we estimate fair value by using assumptions that market participants would use in pricing a debt instrument, including market interest rates, credit standing, yield curves and volatilities. Determining the fair value of the debt component requires the use of accounting estimates and assumptions. These estimates and assumptions are judgmental in nature and could have a significant impact on the determination of the debt component, and the associated non-cash interest expense.

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

Segment Information

We have two operating segments, our Ionis Core segment and Akcea Therapeutics. Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea's stock. After Akcea's IPO, we owned approximately 68 percent of Akcea. We did not change our reportable segments as a result of Akcea's IPO. Akcea is a late-stage biopharmaceutical company focused on developing and commercializing drugs to treat people with serious cardiometabolic diseases caused by lipid disorders. We provide segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviews to assess operating performance and to make operating decisions. We allocate a portion of Ionis' development, R&D support expenses and general and administrative expenses to Akcea for work we performed on behalf of Akcea.

Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in equity securities in publicly held biotechnology companies; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. We classify the majority of our securities as Level 2. We obtain the fair value of our Level 2 investments from our custodian bank or from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. During 2017 and 2016, there were no transfers between our Level 1 and Level 2 investments. When we recognize transfers between levels of the fair value hierarchy, we recognize the transfer on the date the event or change in circumstances that caused the transfer occurs. When we recognize transfers between levels of the fair value hierarchy, we recognize the transfer on the date the event or change in circumstances that caused the transfer occurs. During 2017 and 2016 we did not have any investments that were classified as Level 3 investments.

The following tables present the major security types we held at December 31, 2017 and 2016 that are regularly measured and carried at fair value. The tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At December 31, 2017	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 86,262	$ 86,262	$ —
Corporate debt securities (2)	647,461	—	647,461
Debt securities issued by U.S. government agencies (3)	136,325	—	136,325
Debt securities issued by the U.S. Treasury (3)	30,818	30,818	—
Debt securities issued by states of the U.S. and political subdivisions of the states (4)	93,932	—	93,932
Total	$ 994,798	$ 117,080	$ 877,718

	At December 31, 2016	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 54,137	$ 54,137	$ —
Corporate debt securities (3)	396,221	—	396,221
Debt securities issued by U.S. government agencies (3)	55,179	—	55,179
Debt securities issued by the U.S. Treasury (3)	29,286	29,286	—
Debt securities issued by states of the U.S. and political subdivisions of the states (5)	109,111	—	109,111
Investment in Regulus Therapeutics Inc.	2,414	2,414	—
Total	$ 646,348	$ 85,837	$ 560,511

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

(2) $11.9 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) Included in short-term investments on our consolidated balance sheet.

(4) $3.5 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.

(5) $9.3 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.

Novartis Future Stock Purchase

In January 2017, we and Akcea entered into a SPA with Novartis. As part of the SPA, Novartis was required to purchase $50 million of Akcea's common stock at the IPO price or our common stock at a premium if an IPO did not occur by April 2018. Therefore, at the inception of the SPA, we recorded a $5.0 million asset representing the fair value of the potential future premium we could have received if Novartis purchased our common stock. We determined the fair value of the future premium by calculating the value based on the stated premium in the SPA and estimating the probability of an Akcea IPO. We also included a lack of marketability discount when we determined the fair value of the premium because we would have issued unregistered shares to Novartis if they had purchased our common stock. We measured this asset using Level 3 inputs and recorded it in other assets on our consolidated balance sheet. Because Akcea completed its IPO before April 2018, Novartis will not purchase additional shares of Ionis stock. Therefore, this asset no longer had any value and we wrote-off the remaining balance to other expenses on our third quarter 2017 consolidated statement of operations.

The following is a reconciliation of the potential premium we would have received if Akcea had not completed its IPO, measured at fair value on a recurring basis using significant unobservable inputs (Level 3) for 2017 (in thousands):

	Year Ended December 31, 2017
Beginning balance of Level 3 instruments	$ —
Value of the potential premium we will receive from Novartis at inception of the SPA (January 2017)	5,035
Write-off of premium to other expenses	(5,035)
Ending balance of Level 3 instruments	$ —

Income Taxes

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cuts and Jobs Act of 2017, or the Tax Act. The Tax Act makes broad and complex changes to the U.S. tax code. The changes include, but are not limited to, reducing the U.S. federal corporate tax rate from 35 percent to 21 percent, imposing a mandatory one-time transition tax on certain unrepatriated earnings of foreign subsidiaries, introducing bonus depreciation that will allow for full expensing of qualified property, eliminating the corporate alternative minimum tax, or AMT, and changing how existing AMT credits can be realized, and modifying or repealing many business tax deductions and credits.

The SEC staff issued guidance to address the application of U.S. GAAP in situations when a registrant does not have the necessary information available, prepared, or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of the Tax Act.

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. Valuation allowances are provided when necessary to reduce 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 settlement. The second step is 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 recognize interest and penalties related to unrecognized tax benefits within the income tax expense line in the accompanying consolidated statements of operations. Accrued interest and penalties are included within other long-term liabilities in the consolidated balance sheets.

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. Estimates of future taxable income are based 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 have incurred historical financial statement losses and as a result we had a full valuation allowance recorded against our net deferred tax assets for each of the years in these financial statements. We regularly assess the future realization of our net deferred tax assets and will reduce the valuation allowance in any such period in which we determine that all, or a portion, of our deferred tax assets are 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 May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. Under this guidance, an entity will recognize revenue when it transfers control of promised goods or services to customers in an amount that reflects what the entity expects to receive in exchange for the goods or services. Further an entity will recognize revenue upon satisfying the performance obligation(s) under the related contract. Our performance obligation under our collaboration agreements is typically the research and development activities associated with the delivery of a drug candidate or drug to our partner. Under the current accounting guidance, we recognize revenue from milestone payments we earn under the milestone method from our collaboration agreements. Under the new guidance, the milestone method of revenue recognition is eliminated. Specifically, certain R&D milestone payments we previously recognized in full when we achieved a milestone will now be recognized over a period of time. If we achieve an R&D milestone payment related to activities we are performing under a collaboration agreement, we will recognize the associated revenue from the milestone payment over our estimated performance obligation period. For example, in 2017, we initiated a Phase 1/2a clinical study of IONIS-MAPT$_{Rx}$ in patients with mild Alzheimer's disease. We earned a $10 million milestone payment from Biogen related to the initiation of this study. In 2017, we recognized the entire $10 million as revenue. Under the new standard, we will recognize this milestone payment over the period we are providing R&D services for Biogen. For milestones achieved for which we do not have a continuing performance obligation, we will continue to recognize the milestone payment in its entirety as revenue in the period in which our partner achieves the milestone. For example, in 2017, we earned a $50 million milestone payment from Biogen for the EU approval of SPINRAZA. Under both the new and old standard, we account for this milestone payment the same by recognizing the entire amount upon achievement of the event. This guidance does not change our recognition of commercial revenue from SPINRAZA royalties. We adopted this guidance on January 1, 2018 under the full retrospective approach, which requires us to recast our prior period amounts in the period of adoption.

Our adoption of the standard in 2018 will result in the recognition of additional revenue of approximately $17 million and approximately $27 million for 2017 and 2016, respectively. In addition, our adoption of the standard will result in an increase in our deferred revenue balance of approximately $39 million at December 31, 2017 and a corresponding adjustment to our accumulated deficit for the same amount. Since our collaboration revenue has no associated cost of sales, the impact to our net loss (income) is equal to our revenue adjustment for each period. Additionally, as a result of adopting this new guidance there is no impact to our income tax expense because we have a full valuation allowance. This new guidance also requires additional disclosures about the attributes of our revenue and balances associated with our contracts, which we will include in our first quarter of 2018 financial statements.

In January 2016, the FASB issued amended accounting guidance related to the recognition, measurement, presentation, and disclosure of certain financial instruments. The amended guidance requires us to measure and record equity investments, except those accounted for under the equity method of accounting that have a readily determinable fair value, at fair value and for us to recognize the changes in fair value in our net income (loss), instead of recognizing unrealized gains and losses through accumulated other comprehensive income, as we currently do under the existing guidance. The amended guidance also changes several disclosure requirements for financial instruments, including the methods and significant assumptions we use to estimate fair value. The guidance is effective for fiscal years, and interim periods within that year, beginning after December 15, 2017. We adopted this guidance on January 1, 2018. The adoption of this guidance did not have an impact on our financial results.

In February 2016, the FASB issued amended accounting guidance related to lease accounting, which will require us to record all leases with a term longer than one year on our balance sheet. When we record leases on our balance sheet under the new guidance, we will record a liability with a value equal to the present value of payments we will make over the life of the lease and an asset representing the underlying leased asset. The new accounting guidance requires us to determine if our leases are operating or financing leases. We will record expense for operating type leases on a straight-line basis as an operating expense. If we determine a lease is a financing lease, we will record both interest and amortization expense and generally the expense will be higher in the earlier periods of the lease. The new lease standard is effective for annual and interim periods beginning after December 15, 2018, with early adoption permitted. We must adopt the new standard on a modified retrospective basis, which requires us to reflect our leases on our consolidated balance sheet for the earliest comparative period presented. We plan to adopt this guidance on January 1, 2019. We are currently assessing the effects the new guidance will have on our consolidated financial statements and disclosures.

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. This change will result in us remeasuring our allowance in each reporting period we have credit losses. The new standard is effective for annual and interim periods beginning after December 15, 2019. Early adoption is permitted for periods beginning after December 15, 2018. When we adopt the new standard, we will make any adjustments to beginning balances through a cumulative-effect adjustment to accumulated deficit on that date. We are currently assessing the timing of adoption as well as the effects it will have on our consolidated financial statements and disclosures.

In May 2017, the FASB issued clarifying guidance related to the accounting for modifications of stock-based payment awards. The new guidance is meant to clarify when modification accounting is required. We early adopted this guidance in our financial statements for the quarter ended June 30, 2017 and it did not have an effect on our consolidated financial statements and disclosures.

2. Investments

As of December 31, 2017, we had primarily invested our excess cash in 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.

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2017:

One year or less	71%
After one year but within two years	23%
After two years but within three and one half years	6%
Total	100%

As illustrated above, at December 31, 2017, 94 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, 2017, we had an ownership interest of less than 20 percentin five private companies and one public company with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Dynacure SAS, Kastle Therapeutics, Seventh Sense Biosystems and Suzhou Ribo Life Science CO. The publicly traded company is Antisense Therapeutics Limited, or ATL. We account for our equity investments in the privately-held companies under the cost method of accounting and we account for our equity investment in the publicly traded company at fair value. We record unrealized gains and losses as a separate component of comprehensive income (loss) and include net realized gains and losses in gain (loss) on investments.

During 2015 and 2017, we realized a net gain on our investment in Regulus of $20.2 million and $0.4 million, respectively, when we sold our stock in Regulus.

The following is a summary of our investments (in thousands):

		Gross Unrealized		Estimated
December 31, 2017	**Cost** (1)	**Gains**	**Losses**	**Fair Value**
Available-for-sale securities:				
Corporate debt securities (2)	$ 500,599	$ 2	$ (752)	$ 499,849
Debt securities issued by U.S. government agencies	83,926	—	(212)	83,714
Debt securities issued by the U.S. Treasury	29,428	—	(17)	29,411
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	29,240	4	(122)	29,122
Total securities with a maturity of one year or less	643,193	6	(1,103)	642,096
Corporate debt securities	148,663	8	(1,059)	147,612
Debt securities issued by U.S. government agencies	52,779	—	(168)	52,611
Debt securities issued by the U.S. Treasury	1,409	—	(2)	1,407
Debt securities issued by states of the U.S. and political subdivisions of the states	65,550	—	(740)	64,810
Total securities with a maturity of more than one year	268,401	8	(1,969)	266,440
Total available-for-sale securities	$ 911,594	$ 14	$ (3,072)	$ 908,536

		Gross Unrealized		Estimated
December 31, 2016	**Cost** (1)	**Gains**	**Losses**	**Fair Value**
Available-for-sale securities:				
Corporate debt securities	$ 195,087	$ 25	$ (161)	$ 194,951
Debt securities issued by U.S. government agencies	26,548	—	(10)	26,538
Debt securities issued by the U.S. Treasury	29,298	2	(14)	29,286
Debt securities issued by states of the U.S. and political subdivisions of the states (2)	72,775	2	(134)	72,643
Total securities with a maturity of one year or less	323,708	29	(319)	323,418
Corporate debt securities	202,408	36	(1,174)	201,270
Debt securities issued by U.S. government agencies	28,807	1	(167)	28,641
Debt securities issued by states of the U.S. and political subdivisions of the states	36,816	1	(349)	36,468
Total securities with a maturity of more than one year	268,031	38	(1,690)	266,379
Total available-for-sale securities	$ 591,739	$ 67	$ (2,009)	$ 589,797
Equity securities:				
Regulus Therapeutics Inc.	$ 2,133	$ 281	$ —	$ 2,414
Total equity securities	$ 2,133	$ 281	$ —	$ 2,414
Total available-for-sale and equity securities	$ 593,872	$ 348	$ (2,009)	$ 592,211

(1) Our available-for-sale securities are held at amortized cost.

(2) Includes investments classified as cash equivalents on our consolidated balance sheet.

Investments we consider to be temporarily impaired at December 31, 2017 are as follows (in thousands):

	Number of Investments	Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
		Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	476	$ 551,446	$ (1,236)	$ 74,987	$ (575)	$ 626,433	$ (1,811)
Debt securities issued by U.S. government agencies	45	107,788	(262)	27,538	(118)	135,326	(380)
Debt securities issued by the U.S. Treasury	7	30,818	(19)	—	—	30,818	(19)
Debt securities issued by states of the U.S. and political subdivisions of the states	60	62,519	(545)	24,572	(317)	87,091	(862)
Total temporarily impaired securities	588	$ 752,571	$ (2,062)	$ 127,097	$ (1,010)	$ 879,668	$ (3,072)

We believe that the decline in value of our debt securities is temporary and primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold these securities to maturity. Therefore, we anticipate full recovery of our debt securities' amortized cost basis at maturity.

3. Long-Term Obligations and Commitments

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

	December 31,	
	2017	2016
1 percent convertible senior notes	$ 533,111	$ 500,511
Long-term mortgage debt	59,771	—
Long-term financing liability for leased facility	—	72,359
Principal balance of fixed rate note with Morgan Stanley	12,500	12,500
Leases and other obligations	2,095	3,735
Total	$ 607,477	$ 589,105
Less: current portion	(1,621)	(1,185)
Total Long-Term Obligations	$ 605,856	$ 587,920

Convertible 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 raised $487 million of proceeds, net of issuance costs. We used a substantial portion of the net proceeds from the issuance of the 1 percent convertible senior notes to repurchase $140 million in principal of our 2¾ percent convertible senior notes at a price of $441.9 million, including accrued interest. As a result, the new principal balance of the 2¾ percent notes was $61.2 million.

In December 2016, we issued an additional $185.5 million of 1 percent convertible senior notes in exchange for the redemption of $61.1 million of our 2¾ percent convertible senior notes. As a result of the debt exchange we completed in December 2016, we recorded a $4.0 million non-cash loss on early retirement of debt, reflecting the early retirement of the majority of our remaining 2¾ percent convertible notes in December 2016.

At December 31, 2017, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At December 31, 2017 we had the following 1 percent convertible senior notes outstanding (amounts in millions except price per share data):

	1 Percent Convertible Senior Notes
Outstanding balance	$ 685.5
Original issue date ($500 million of principal)	November 2014
Additional issue date ($185.5 million of principal)	December 2016
Maturity date	November 2021
Interest rate	1 percent
Conversion price per share	$ 66.81
Total shares of common stock subject to conversion	10.3

Interest is payable semi-annually in arrears on May 15 and November 15 of each year for the 1 percent notes. The 1 percent 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 notes are initially convertible into approximately 10.3 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 percent 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 percent 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.

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 Percent Convertible Senior Notes Issued in November 2014	1 Percent Convertible Senior Notes Issued in December 2016
Nonconvertible debt borrowing rate	7.4 percent	6.8 percent
Effective interest rate	7.8 percent	7.2 percent
Amortization period of debt discount	7 years	5 years

Interest expense for the year ended December 31, 2017, 2016 and 2015 included $32.5 million, $25.1 million and $23.2 million, respectively, of non-cash interest expense related to the amortization of the debt discount and debt issuance costs for our convertible notes.

The following table summarizes information about the equity and liability components of our outstanding 1 percent convertible notes (in thousands). We measured the fair values of the convertible notes outstanding based on quoted market prices, which is a Level 2 measurement:

	December 31,	
	2017	2016
Fair value of outstanding notes	$ 727,420	$ 700,969
Principal amount of convertible notes outstanding	$ 685,450	$ 685,450
Unamortized portion of debt discount	$ 144,112	$ 175,699
Long-term debt	$ 533,111	$ 500,511
Carrying value of equity component	$ 219,011	$ 219,011

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. We amended the credit agreement in February 2016 to increase the amount available for us to borrow. Under the amended credit agreement, we can borrow up to a maximum of $30 million of revolving credit for general working capital purposes. Under the credit agreement interest is payable monthly in arrears on the outstanding principal at a borrowing rate based on our option of:

(i) a floating rate equal to the one-month London Interbank Offered Rate, or LIBOR, in effect plus 1.25 percent per annum;
(ii) a fixed rate equal to LIBOR plus 1.25 percent for a period of one, two, three, four, six, or twelve months as elected by us; or
(iii) a fixed rate equal to the LIBOR swap rate during the period of the loan.

Additionally, after June 1, 2016, we pay 0.25 percent per annum, payable quarterly in arrears, for any amount unused under the credit facility. As of December 31, 2017, we had $12.5 million in outstanding borrowings under the credit facility with a 2.31 percent fixed interest rate and a maturity date of September 2019, which we used to fund our capital equipment needs and is consistent with our historical practice to finance these costs.

The credit agreement includes customary affirmative and negative covenants and restrictions. We are in compliance with all covenants of the credit 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. As a result of the purchase, we extinguished the financing liability we had previously recorded on our balance sheet. The difference between the purchase price of the facility and the carrying value of our financing liability at the time of the purchase was $7.7 million. We recognized this amount as a non-cash loss on extinguishment of financing liability for leased facility in our consolidated results of operations in the third quarter of 2017.

We also purchased our manufacturing facility in July 2017 for $14.0 million. We previously accounted for the lease on this facility as an operating lease. We capitalized the purchase price of the building as a fixed asset in the third quarter of 2017.

We financed the purchase of our primary R&D facility and our manufacturing facility, with mortgage debt of $51.3 million and $9.1 million, respectively. 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, 2017 are as follows (in thousands):

2018	$ 9,617
2019	22,082
2020	9,330
2021	694,774
2022	2,809
Thereafter	71,603
Subtotal	$ 810,215
Less: current portion	(53)
Less: fixed and determinable interest	(51,465)
Less: unamortized portion of debt discount	(144,791)
Plus: Deferred rent	165
Total	$ 614,071

Operating Leases

We lease a facility adjacent to our manufacturing facility that has laboratory and office space that we use to support our manufacturing facility. We lease this space under a non-cancelable operating lease with an initial term ending in June 2021 and an option to extend the lease for up to two five-year periods. Additionally, Akcea leases office space in a building in Cambridge, Massachusetts. A portion of Akcea's operating lease expires in July 2018, with the other portion expiring in April 2020. We also lease office equipment under non-cancelable operating leases with terms through January 2021.

Annual future minimum payments under operating leases as of December 31, 2017 are as follows (in thousands):

	Operating Leases
2018	$ 864
2019	636
2020	477
2021	147
Total minimum payments	$ 2,124

Rent expense was $1.7 million for the year ended December 31, 2017. Rent expense was $2.0 million for each of the years ended December 31, 2016 and 2015. We recognized rent expense on a straight line basis over the lease term for the lease on our manufacturing facility, the lease on our building adjacent to our manufacturing facility and Akcea’s office space, which resulted in a deferred rent balance of $0.1 million and $2.1 million at December 31, 2017 and 2016, respectively.

4. Stockholders’ Equity

Preferred Stock

We are authorized to issue up to 15,000,000 shares of “blank check” Preferred Stock. As of December 31, 2017, 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, 2017.

Common Stock

At December 31, 2017 and 2016, we had 300,000,000 shares of common stock authorized, of which 124,976,373 and 121,636,273 were issued and outstanding, respectively. As of December 31, 2017, total common shares reserved for future issuance were 18,419,727.

During the years ended December 31, 2017, 2016 and 2015, we issued 1,706,000, 1,285,000 and 1,908,000 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 $22.9 million, $13.7 million and $24.9 million in 2017, 2016 and 2015, respectively.

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 20,000,000 shares of common stock to our employees, directors, and consultants. The plan expires in January 2024. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. At December 31, 2017, a total of 1,603,403 options were outstanding, of which options to purchase 1,553,252 shares were exercisable, and 31,878 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 and in May 2017, 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 5,500,000 to 11,000,000 in June 2015 and from 11,000,000 to 16,000,000 in May 2017. The plan expires in June 2021. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only options and restricted stock unit awards to our employees, directors and consultants. Under the 2011 Plan, stock options cannot vest in a period of less than two years and restricted stock unit awards cannot vest in a period of less than three years. We have granted restricted stock unit awards to our employees under the 2011 Plan which vest annually over a four-year period. At December 31, 2017, a total of 7,120,643 options were outstanding, of which 3,201,717 were exercisable, 821,771 restricted stock unit awards were outstanding, and 6,822,389 shares were available for future grant under the 2011 Plan.

Under the 2011 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur. The stock options and restricted stock unit awards we issue to our chief executive officer and issued to B. Lynne Parshall in her former role as chief operating officer will accelerate upon a change of control, as defined in the 2011 Plan.

Corporate Transactions and Change in Control under 2011 Plan

In the event of certain significant corporate transactions, our Board of Directors has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 Plan:

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and
- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options and restricted stock units to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan (the 2002 Plan). In June 2015, after receiving approval from our stockholders, we amended our 2002 Non-Employee Directors Stock Option Plan to increase the total number of shares reserved for issuance. We increased the shares available under our 2002 Non-Employee Directors Stock Option Plan from 1,200,000 to 2,000,000. Options under this plan expire ten years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2017, a total of 672,750 options were outstanding, of which 427,125 were exercisable, 40,933 restricted stock unit awards were outstanding, and 635,867 shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In June 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 3,524,596 shares authorized under the plan as of December 31, 2017. The ESPP permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10 percent of each employee's compensation) at the lower of 85 percent of fair market value at the beginning of the purchase period or the end of each six-month 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 2017, employees purchased and we issued to employees 67,481 shares under the ESPP at a weighted average price of $27.51 per share. At December 31, 2017, there were 668,232 shares available for purchase under the ESPP.

Stock Option Activity

The following table summarizes the stock option activity for the year ended December 31, 2017 (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, 2016	9,178	$ 40.48		
Granted	3,274	$ 47.76		
Exercised	(1,345)	$ 15.74		
Cancelled/forfeited/expired	(1,710)	$ 51.71		
Outstanding at December 31, 2017	9,397	$ 44.52	4.42	$ 92,288
Exercisable at December 31, 2017	5,182	$ 39.10	3.33	$ 80,167

The weighted-average estimated fair values of options granted were $25.42, $26.72 and $27.44 for the years ended December 31, 2017, 2016 and 2015, respectively. The total intrinsic value of options exercised during the years ended December 31, 2017, 2016 and 2015 were $49.5 million, $28.0 million and $84.7 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $21.2 million, $12.6 million and $23.6 million for the years ended December 31, 2017, 2016 and 2015, respectively. For the year ended December 31, 2017, the weighted-average fair value of options exercised was $52.53. As of December 31, 2017, total unrecognized compensation cost related to non-vested stock-based compensation plans was $75.2 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.2 years.

Restricted Stock Unit Activity

The following table summarizes the RSU activity for the year ended December 31, 2017 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2016	778	$ 47.68
Granted	420	$ 48.88
Vested	(296)	$ 43.79
Cancelled/forfeited	(39)	$ 48.90
Non-vested at December 31, 2017	863	$ 49.55

For the years ended December 31, 2017, 2016 and 2015, the weighted-average grant date fair value of RSUs granted was $48.88, $41.79 and $65.69 per RSU, respectively. As of December 31, 2017, total unrecognized compensation cost related to RSUs was $16.5 million. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures. We expect to recognize this cost over a weighted average period of 1.2 years.

Stock-based Compensation Expense and Valuation Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2017, 2016 and 2015 (in thousands), which was allocated as follows and includes $17.5 million, $10.1 million and $6.5 million of stock-based compensation expense for Akcea employees in 2017, 2016 and 2015, respectively:

	Years Ended December 31,		
	2017	2016	2015
Research, development and patent	$ 64,521	$ 55,099	$ 43,638
Selling, general and administrative	21,454	17,009	15,676
Total	$ 85,975	$ 72,108	$ 59,314

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, 2017, 2016 and 2015, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	December 31,		
	2017	**2016**	**2015**
Risk-free interest rate	1.8%	1.5%	1.5%
Dividend yield	0.0%	0.0%	0.0%
Volatility	65.9%	58.7%	53.8%
Expected life	4.5 years	4.5 years	4.5 years

Board of Director Stock Options:

	December 31,		
	2017	**2016**	**2015**
Risk-free interest rate	2.2%	1.3%	2.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	61.2%	53.1%	52.2%
Expected life	6.6 years	6.5 years	6.9 years

ESPP:

	December 31,		
	2017	**2016**	**2015**
Risk-free interest rate	0.8%	0.4%	0.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	59.9%	86.4%	51.7%
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. Our historical forfeiture estimates have not been materially different from our actual forfeitures.

5. Income Taxes

Loss before income tax (benefit) expense is comprised of (in thousands):

	Years Ended December 31,		
	2017	**2016**	**2015**
United States	$ (11,802)	$ (83,622)	$ (87,906)
Foreign	(11,474)	—	—
Loss before income tax (benefit) expense	$ (23,276)	$ (83,622)	$ (87,906)

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

	Years Ended December 31,		
	2017	2016	2015
Current:			
Federal	$ (7,460)	$ 1,067	$ 379
State	1,246	1,867	(7)
Foreign	234	—	—
Total current income tax (benefit) expense	(5,980)	2,934	372
Deferred:			
Federal	—	—	—
State	—	—	—
Total deferred income tax (benefit) expense	—	—	—
Total income tax (benefit) expense	$ (5,980)	$ 2,934	$ 372

The reconciliation between our effective tax rate on loss from continuing operations and the statutory U.S. tax rate is as follows (in thousands):

	Years Ended December 31,					
	2017		2016		2015	
Pre-tax loss	$ (23,276)		$ (83,622)		$ (87,906)	
Statutory rate	(8,147)	35.0%	(29,268)	35.0%	(30,767)	35.0%
State income tax net of federal benefit	722	(3.1)%	(276)	0.3%	1	0.0%
Foreign	4,299	(18.3)%	—	0.0%	—	0.0%
Net change in valuation allowance	(76,409)	328.3%	55,927	(66.9)%	69,499	(79.1)%
Net operating loss expiration	3,987	(17.0)%	—	0.0%	—	0.0%
Tax credits	(32,769)	140.8%	(26,954)	32.2%	(41,284)	47.0%
Deferred tax true-up	4,848	(20.6)%	2,591	(3.1)%	1,496	(1.7)%
Tax Cuts and Jobs Act	107,323	(461.1)%	—		—	0.0%
Nondeductible items	4,123	(17.9)%	1,149	(1.4)%	1,055	(1.2)%
Akcea deconsolidation adjustment at IPO	469	(2.0)%	—	0.0%	—	0.0%
Excess stock-based compensation	(14,337)	61.0%	—	0.0%	—	0.0%
Other	(89)	0.6%	(235)	0.4%	372	(0.4)%
Effective rate	$ (5,980)	25.7%	$ 2,934	(3.5)%	$ 372	(0.4)%

Significant components of our deferred tax assets and liabilities as of December 31, 2017 and 2016 are as follows (in thousands):

	Years Ended December 31,	
	2017	2016
Deferred Tax Assets:		
Net operating loss carryovers	$ 153,575	$ 194,372
R&D credits	240,290	193,845
Deferred revenue	42,055	54,203
Stock-based compensation	40,090	48,209
Intangible and capital assets	672	—
Other	12,164	26,228
Total deferred tax assets	$ 488,846	$ 516,857
Deferred Tax Liabilities:		
Convertible debt	$ (32,391)	$ (62,669)
Intangible and capital assets	—	(2,030)
Net deferred tax asset	$ 456,455	$ 452,158
Valuation allowance	(456,455)	(452,158)
Total net deferred tax assets and liabilities	$ —	$ —

In accordance with the SEC guidance, we provided our best estimate of the impact of the Tax Act in the period ended December 31, 2017 based on our understanding of the Tax Act and guidance available as of the date of this filing. We remeasured our existing net U.S. deferred tax assets using the enacted rate and other known existing changes to the tax code. This resulted in a total decrease in these assets by $107.3 million which was fully offset by a decrease in the valuation allowance. In addition, we recorded a $7.7 million tax benefit related to our cumulative prior year AMT tax credit carryovers, which are now reflected as part of a long-term income tax receivable because under the Tax Act, AMT credits are refundable from 2018 through 2021.We also assessed the impact of the deemed repatriation of foreign earnings and the impact of the limitation on tax deductions for executive compensation under the applicable section of the tax code. We have recognized provisional amounts in our financial statements for these and other items. The ultimate impact may differ materially from these provisional amounts due to, among other things, additional analysis, changes in our interpretations and assumptions, additional regulatory guidance that may be issued, and other actions we may take as a result of the Tax Act.

At December 31, 2017, we had federal and California tax net operating loss carryforwards of approximately $561.1 million and $887.1 million, respectively. Our federal tax loss carryforwards will begin to expire in 2024, unless we use them before then. Our California loss carryforwards continued to expire in 2017. At December 31, 2017 we also had federal and California research and development tax credit carryforwards of approximately $233.3 million and $56.2 million, respectively. Our Federal research and development tax credit carryforwards begin to expire in 2018. 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 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 have incurred historical financial statement losses since inception and as a result we have a full valuation allowance recorded against our net deferred tax assets. We regularly assess the future realization of our net deferred tax assets and will reduce the valuation allowance in any such period in which we determine that all, or a portion, of our deferred tax assets are more-likely-than-not to be realized.

Our valuation allowance increased by $4.3 million from December 31, 2016 to December 31, 2017. The net increase relates to increases from current year activity, offset by a decrease related to the remeasurement of our net deferred tax assets as required by the Tax Act.

Historically, we recognized excess tax benefits associated with stock-based compensation to stockholders' equity only when realized. We followed the with-and-without approach excluding any indirect effects of the excess tax deductions to determine when we should realize excess tax benefits relating to stock-based compensation. Under this approach, we did not realize our excess tax benefits related to stock-based compensation until after we utilize all our other tax benefits available to us. During the year ended December 31, 2016, we realized $1.9 million of such excess tax benefits, and accordingly, we recorded a corresponding credit to additional paid-in capital.

In March 2016, the FASB issued amended guidance to simplify certain aspects of accounting for stock-based payments. We adopted this amended guidance on January 1, 2017. Under the amended guidance, we recognize all excess tax benefits and tax deficiencies as income tax expense or benefit in the period in which they occur.

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):

	Years Ended December 31,		
	2017	**2016**	**2015**
Beginning balance of unrecognized tax benefits	$ 66,999	$ 51,257	$ 27,365
Settlement of prior period tax positions	—	(4,033)	—
Increase for prior period tax positions	1,520	7,928	215
Increase for current period tax positions	9,495	11,847	23,677
Ending balance of unrecognized tax benefits	$ 78,014	$ 66,999	$ 51,257

Included in the balance of unrecognized tax benefits at December 31, 2017, is $63.6 million that could impact our effective tax rate, if recognized. None of the unrecognized tax benefits currently impact our effective tax rate due to the full valuation allowance we have recorded against our deferred tax assets.

We do not foresee any material changes to our gross unrecognized tax benefits within the next twelve months.

We recognize interest and/or penalties related to income tax matters in income tax expense. We did not recognize any accrued interest and penalties related to gross unrecognized tax benefits during the year ended December 31, 2017.

Due to the carryforward of unutilized net operating losses and research and development credits, we are subject to taxation in the United States and various state jurisdictions. Our tax years for 1998 through 2016 are subject to examination by the U.S. tax authorities and our tax years for 2003 through 2016 are subject to examination by the California 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.

6. Collaborative Arrangements and Licensing Agreements

Strategic Partnerships

AstraZeneca

Cardiometabolic and Renal Diseases Collaboration

In July 2015, we and AstraZeneca formed a strategic collaboration to discover and develop antisense therapies for treating cardiovascular and metabolic diseases primarily focused on targets in the kidney and renal diseases. As part of the agreement, we granted AstraZeneca an exclusive license to IONIS-AZ4-2.5-L_{Rx}, a drug we designed to treat cardiovascular disease and our first drug that combines our Generation 2.5 and LIgand-Conjugated Antisense, or LICA, technology. We also granted AstraZeneca the option to license a drug for each additional target advanced under this research collaboration. In February 2018, AstraZeneca licensed a second drug under our collaboration, IONIS-AZ5-2.5$_{Rx}$, a drug we designed to treat a genetically associated form of kidney disease. AstraZeneca is responsible for all further global development, regulatory and commercialization activities and costs for IONIS-AZ4-2.5-L_{Rx} and IONIS-AZ5-2.5$_{Rx}$ and any other future drug development candidates AstraZeneca accepts.

Under the terms of the agreement, we received a $65 million upfront payment. Since this agreement has multiple elements, we evaluated the deliverables in this arrangement and determined that none of the deliverables have stand-alone value because of the early stage of research for this collaboration. Therefore, we concluded there is one unit of accounting and we are amortizing the $65 million upfront payment through August 2021. We are eligible to receive license fees and substantive milestone payments of up to more than $4 billion as drugs under this collaboration advance, including up to $1.1 billion for the achievement of development milestones and up to $2.9 billion for regulatory milestones. From inception through December 2017, we have received $93 million in upfront fees, milestone payments, and other payments under this cardiometabolic and renal diseases collaboration, including a $25 million milestone payment we received when we moved the first development candidate into preclinical development, IONIS-AZ4-2.5-L_{Rx} in December 2016. Additionally, in February 2018, we earned $30 million when AstraZeneca licensed IONIS-AZ5-2.5$_{Rx}$. We will earn the next milestone payment of $10 million under this collaboration if we advance a drug under our cardiometabolic research program with AstraZeneca. In addition, we are eligible to receive tiered royalties up to the low teens on sales from any product that AstraZeneca successfully commercializes under this collaboration agreement.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense drugs to treat cancer. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize IONIS-STAT3-2.5$_{Rx}$ for the treatment of cancer and an option to license up to three anti-cancer drugs under separate research programs. AstraZeneca is responsible for all global development, regulatory and commercialization activities for IONIS-STAT3-2.5$_{Rx}$. We and AstraZeneca have evaluated IONIS-STAT3-2.5$_{Rx}$ in people with advanced metastatic hepatocellular carcinoma and advanced lymphoma. AstraZeneca is evaluating IONIS-STAT3-2.5$_{Rx}$ in combination with Imfinzi (durvalumab), AstraZeneca's programmed death ligand (PD-L1) blocking drug, in people with head and neck cancer. Under the research program, we are responsible for identifying a development candidate for each of the three anti-cancer research programs. AstraZeneca has the option to license drugs resulting from each of the three anti-cancer research programs, and if AstraZeneca exercises its option for a drug, it will be responsible for all further global development, regulatory and commercialization activities and costs for such drug. The first development candidate identified under the anti-cancer research program was IONIS-KRAS-2.5$_{Rx}$, which AstraZeneca licensed from us in December 2016. IONIS-KRAS-2.5$_{Rx}$ is a Generation 2.5 antisense drug we designed to directly target KRAS, one of the most frequently mutated genes in cancer.

Under the terms of the agreement, we received $31 million in upfront payments. We recorded revenue of $11.5 million upon receipt of these payments and we have amortized $11.9 million into revenue as we have performed development activities under this collaboration. We recognized the remaining $7.6 million related to the option to license three drugs under the research program through February 2018. In January 2016, we and AstraZeneca amended the agreement for the research program. Under the amended terms of the agreement, we can earn an additional $5 million in milestone payments for advancing a drug under our research program.

We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. In addition, we are eligible to receive tiered royalties up to the low to mid-teens on sales from any drugs resulting from these programs. If AstraZeneca successfully develops IONIS-STAT3-2.5$_{Rx}$, IONIS-KRAS-2.5$_{Rx}$ and two other drugs under the research program, we could receive license fees and substantive milestone payments of up to more than $750 million, including up to $226 million for the achievement of development milestones and up to $485 million for the achievement of regulatory milestones. From inception through December 2017, we have received $97.8 million in upfront fees, milestone payments, and other payments under this oncology collaboration. We will earn the next milestone payment of $17.5 million if we advance a drug under our cancer research program with AstraZeneca.

Each of our agreements with AstraZeneca will continue until the expiration of all payment obligations under the applicable agreement. In addition, the agreement, or any program under the applicable agreement, may terminate early under the following situations:

- AstraZeneca may terminate the agreement or any program at any time by providing written notice to us;
- AstraZeneca may terminate the agreement or any program by providing written notice if we undergo a change of control with a third party; and
- Either we or AstraZeneca may terminate the agreement or any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During 2017, 2016 and 2015 we earned revenue of $13.8 million, $64.9 million and $6.4 million, respectively, from our relationship with AstraZeneca, which represented three percent, 19 percent and two percent, respectively, of our total revenue for those periods. Our balance sheets at December 31, 2017 and 2016 included deferred revenue of $41.8 million and $51.5 million, respectively, related to our relationship with AstraZeneca.

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 drugs with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved drug to treat people with spinal muscular atrophy, or SMA. Additionally, we and Biogen are currently developing six other drugs to treat neurodegenerative diseases under these collaborations, including IONIS-SOD1$_{Rx}$ for ALS, IONIS-MAPT$_{Rx}$ (formerly IONIS-BIIB4$_{Rx}$) for Alzheimer's disease and IONIS-C9$_{Rx}$ (formerly IONIS-BIIB5$_{Rx}$), IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ to treat undisclosed neurodegenerative diseases. In addition to these drugs, we and Biogen are evaluating numerous additional targets to develop drugs to treat neurological diseases. Most recently, in December 2017 we entered into a collaboration with Biogen to identify new antisense drugs for the treatment of SMA. From inception through December 2017, we have received nearly $745 million from our Biogen 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. In December 2016, the FDA approved SPINRAZA for the treatment of SMA in pediatric and adult patients. In January 2018, Biogen reported that SPINRAZA was available in over 30 global markets.

Our 2017 revenue included $112.5 million in commercial revenue from SPINRAZA royalties. In addition to SPINRAZA royalties, from inception through December 2017, we have received $436 million in payments for advancing SPINRAZA, including $90 million of milestone payments for the approval of SPINRAZA in the EU and Japan we earned during 2017. We are receiving tiered royalties up to the mid-teens on any sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We paid Cold Spring Harbor Laboratory and the University of Massachusetts nominal amounts for license fees and milestone payments we received in 2017. We also pay a low single digit royalty on sales of SPINRAZA. Additionally, we owe a low single digit royalty on future sales of SPINRAZA. Biogen is responsible for all further global development, regulatory and commercialization activities and costs for SPINRAZA.

New antisense drugs for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense drugs for the treatment of SMA. Biogen will have the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for all further global development, regulatory and commercialization activities and costs for such therapies. Under the collaboration agreement, we received a $25 million upfront payment in December 2017, which we plan to amortize through December 2019. We will earn development and regulatory substantive milestone payments from Biogen if new drugs 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, substantive 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 $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 earn the next milestone payment of up to $45 millionfor the initiation of a Phase 3 study for a drug under this collaboration.

Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense drugs to up to three targets to treat neurodegenerative diseases. We are responsible for the development of each of the drugs through the completion of the initial Phase 2 clinical study for such drug. Biogen has the option to license a drug from each of the three programs through the completion of the first Phase 2 study for each program. We are currently advancing IONIS-MAPT$_{Rx}$ (formerly IONIS-BIIB4$_{Rx}$) for Alzheimer's disease under this collaboration. If Biogen exercises its option for a drug, it will assume all further global development, regulatory and commercialization responsibilities and costs for that drug.

Under the terms of the agreement, we received an upfront payment of $30 million, which we are amortizing through December 2020. Over the term of the collaboration, we are eligible to receive up to $210 million in a license fee and substantive milestone payments per program, plus a mark-up of the cost estimate of the Phase 1 and 2 studies. We are eligible to receive up to $10 million in development milestone payments to support research and development of each program, plus a mark-up of the cost estimate of the Phase 1 and 2 studies. We are also eligible to receive up to $130 million in milestone payments per program if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any drugs resulting from each of the three programs. From inception through December 2017, we have received $56 million in milestone payments and upfront fees under this collaboration, including $10 million milestone payment we received in 2017 for the initiation of a Phase 1/2a study of IONIS-MAPT$_{Rx}$. We will earn the next milestone payment of $7.5 million if we continue to advance IONIS-MAPT$_{Rx}$.

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 drugs resulting from this collaboration. The exclusivity for neurological diseases will last through September 2019, and may be extended for any drug development programs Biogen is pursuing under the collaboration. We will usually be responsible for drug discovery and early development of antisense drugs and Biogen will have the option to license antisense drugs 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 for a drug, it will assume all further global development, regulatory and commercialization responsibilities and costs for that drug. We are currently advancing five drugs, IONIS-SOD1$_{Rx}$, IONIS-C9$_{Rx}$ (formerly IONIS-BIIB5$_{Rx}$), IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ under this collaboration. Biogen will be responsible for all of the drug discovery and development activities for drugs using other modalities.

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 drugs developed through this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. If we have a change of control during the first six years of the collaboration, we may be required to refund Biogen a portion of the $100 million upfront payment, with the amount of the potential refund decreasing ratably as we progress through the initial six-year term of the collaboration. We are amortizing the $100 million upfront payment through September 2019. Because the amortization period for the upfront payment will never be less than the initial six-year term of the collaboration, the amount of revenue we recognize from the upfront payment will never exceed the amount that Biogen could potentially require us to refund.

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 substantive milestone payments. We are eligible to receive up to approximately $60 million for the achievement of research and development milestones, including amounts related to the cost of clinical trials, and up to $130 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any antisense drugs developed under this collaboration. If other modalities are chosen, such as small molecules or monoclonal antibodies, we are eligible to receive up to $90 million in substantive milestone payments, including up to $35 million for the achievement of research and development milestones and up to $55 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered single-digit royalties on sales from any drugs using non-antisense modalities developed under this collaboration. From inception through December 2017, we have received $165 million in upfront fees, milestone payments and other payments under this collaboration, including $15 million in milestone payments we received in 2017 for validating two undisclosed neurological disease targets. We will earn the next milestone payment of up to $10 million if we advance a program under this collaboration.

Each of our agreements with Biogen will continue until the earlier of the date all of Biogen's options to obtain the exclusive licenses under the applicable agreement expire unexercised or, if Biogen exercises its option, until the expiration of all payment obligations under the applicable agreement. In addition, each agreement, or any program under an agreement, may terminate early under the following situations:

- Biogen may terminate the agreement or any program at any time by providing written notice to us;
- Under specific circumstances, if we are acquired by a third party with a product that directly competes with a compound being developed under the agreement, Biogen may terminate the affected program by providing written notice to us;
- If, within a specified period of time, any required clearance of a transaction contemplated by an agreement under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, is not received, then either we or Biogen may terminate the affected program by providing written notice to the other party; and
- Either we or Biogen may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During 2017, 2016 and 2015, we earned revenue of $259.8 million, $207.9 million and $106.2 million, respectively, from our relationship with Biogen, which represented 51 percent, 60 percent and 37 percent, respectively, of our total revenue for those periods. Our balance sheets at December 31, 2017 and 2016 included deferred revenue of $69.3 million and $67.5 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

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. We recorded revenue of $91.2 million related to the license for IONIS-FXI$_{Rx}$ in June 2015 and we recognized the majority of the remaining amount related to development activities for IONIS-FXI$_{Rx}$ through November 2016.

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. We recorded revenue of $64.9 million related to the license for IONIS-FXI-L$_{Rx}$ in February 2017, and we are recognizing the remaining amount over the period we are performing the ongoing development activities for IONIS-FXI-L$_{Rx}$ and IONIS-FXI$_{Rx}$ through May 2019. We are conducting a Phase 2b study evaluating IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, we plan to develop IONIS-FXI-L$_{Rx}$ through Phase 1. Following these studies and Bayer's decision to further advance these programs, Bayer will be responsible for all global development, regulatory and commercialization activities and costs for both drugs. We are eligible to receive additional milestone payments as each drug advances toward the market. In total over the term of our collaboration, we are eligible to receive up to $385 million in license fees, substantive 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 drugs combined. From inception through December 2017, we have received over $175 million from our Bayer collaboration. We will earn the next milestone payment of $10 million if we advance a program under this collaboration.

Our agreement with Bayer will continue until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- Bayer may terminate the agreement or any program at any time by providing written notice to us;
- Either we or Bayer may terminate the agreement or any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During 2017, 2016 and 2015 we earned revenue of $69.2 million, $5.4 million and $93.4 million, respectively, from our relationship with Bayer, which represented 14 percent, two percent and 33 percent, respectively, of our total revenue for those periods. Our consolidated balance sheet at December 31, 2017 and 2016 included deferred revenue of $7.3 million and $1.4 million, respectively, related to our relationship with Bayer.

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new drugs against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. Under the terms of the agreement, we received $38 million in upfront and expansion payments, which we amortized through September 2017.

In August 2017, as part of a reprioritization of its pipeline and strategic review of its Rare Diseases business, GSK declined its options for inotersen, our Phase 3 drug to treat people with TTR amyloidosis and IONIS-FB-L_{Rx} (formerly IONIS-GSK4-L_{Rx}), an antisense drug to treat complement-mediated diseases. We are continuing to advance each of these drugs independently.

GSK, consistent with its focus on treatments for infectious diseases, continues to advance two drugs targeting hepatitis B virus, or HBV, under our collaboration: IONIS-HBV_{Rx} and IONIS-HBV-L_{Rx}. GSK is currently conducting Phase 2 studies for both of these drugs, which we designed to reduce the production of viral proteins associated with HBV infection. In March 2016, we and GSK amended the development plan for IONIS-HBV_{Rx} to allow GSK to conduct all further development activities for this program. GSK has the exclusive option to license the drugs resulting from this alliance at Phase 2 proof-of-concept for a license fee.

Under our agreement, if GSK successfully develops these drugs and achieves pre-agreed sales targets, we could receive license fees and substantive milestone payments of $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. From inception through December 2017, we have received more than $162 million in payments under this alliance with GSK. We will earn the next milestone payment of up to $15 million for the initiation of a Phase 3 study for the HBV program. In addition, we are eligible to receive tiered royalties up to the mid-teens on sales from any product that GSK successfully commercializes under this alliance.

Our alliance with GSK will continue until the earlier of the date that all of GSK's options to obtain the exclusive licenses under the agreement expire unexercised or, if GSK exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- GSK may terminate any program, at any time by providing written notice to us; and
- Either we or GSK may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement with respect to the affected program, or the entire agreement if the other party becomes insolvent.

During 2017, 2016 and 2015, we earned revenue of $8.6 million, $12.3 million and $33.3 million respectively, from our relationship with GSK, which represented two percent, four percent and 12 percent, respectively, of our total revenue for those years. Our balance sheet at December 31, 2016 included deferred revenue of $2.1 million, related to our relationship with GSK.

Janssen Biotech, Inc.

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders of the gastrointestinal tract. Janssen has the option to license drugs from us through the designation of a development candidate for up to three programs. Prior to option exercise we are responsible for the discovery activities to identify a development candidate. If Janssen exercises an option for one of the programs, it will be responsible for the global development, regulatory and commercial activities under that program. Under the terms of the agreement, we received $35 million in upfront payments, which we amortized through November 2017. We are eligible to receive up to more than $800 million in license fees and substantive milestone payments for these programs, including up to $175 million for the achievement of development milestones, up to $440 million for the achievement of regulatory milestones and up to $180 million for the achievement of commercialization milestones. From inception through December 2017, we have received $61.8 million, including $15 million in license fees when Janssen licensed IONIS-JBI1-2.5_{Rx} and IONIS-JBI2-2.5_{Rx} from us in 2016 and 2017, respectively. We also received $5 million in January 2018 for the initiation of a Phase 1 study of IONIS-JBI1-2.5_{Rx} in late 2017. In addition, we are eligible to receive tiered royalties up to the near teens on sales from any drugs resulting from this collaboration. We will earn the next milestone payment of $5 million if Janssen chooses another target to advance under this collaboration.

Our agreement with Janssen will continue until the earlier of the date that all of Janssen's options to obtain the exclusive licenses under the agreement expire unexercised or, if Janssen exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement, or any program under the agreement, may terminate early under the following situations:

- Janssen may terminate the agreement or any program at any time by providing written notice to us; and
- Either we or Janssen may terminate any program by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement, or the entire agreement if the other party becomes insolvent.

During 2017, 2016 and 2015 we earned revenue of $33.5 million, $27.3 million and $8.9 million, respectively, from our relationship with Janssen. Our balance sheet at December 31, 2016 included deferred revenue of $17.5 million related to our relationship with Janssen.

Novartis

In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the collaboration agreement, Novartis has an exclusive option to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Akcea is responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the FDA and providing API for each drug. If Novartis exercises an option for one of these drugs, Novartis will be responsible for all further global development, regulatory and commercialization activities and costs for such drug.

Akcea received a $75 million upfront payment in the first quarter of 2017, of which it retained $60 million and paid us $15 million as a sublicense fee. If Novartis exercises its option for a drug, Novartis will pay Akcea a license fee equal to $150 million for each drug it licenses. In addition, for AKCEA-APO(a)-L_{Rx}, Akcea is eligible to receive up to $600 million in substantive 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 $285 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L_{Rx}, Akcea is eligible to receive up to $530 million in substantive milestone payments, including $25 million for the achievement of a development milestone, up to $240 million for the achievement of regulatory milestones and up to $265 million for the achievement of commercialization milestones. Akcea plans to co-commercialize any licensed drug commercialized by Novartis in selected markets, under terms and conditions that it plans to negotiate with Novartis in the future, through the specialized sales force Akcea is building to commercialize volanesorsen. Following Novartis' exercise of its option for either drug, Akcea will earn the next milestone payment of $25 million if Novartis advances the Phase 3 study for either drug. Akcea is also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Akcea will pay 50 percent of these license fees, milestone payments and royalties to us as a sublicense fee.

The agreement with Novartis will continue until the earlier of the date that all of Novartis' options to obtain the exclusive licenses under the agreement expire unexercised or, if Novartis exercises its options, until the expiration of all payment obligations under the agreement. In addition, the agreement as a whole or with respect to any drug under the agreement, may terminate early under the following situations:

- Novartis may terminate the agreement as a whole or with respect to any drug at any time by providing written notice to us;
- Either we or Novartis may terminate the agreement with respect to any drug by providing written notice to the other party in good faith that we or Novartis has determined that the continued development or commercialization of the drug presents safety concerns that pose an unacceptable risk or threat of harm in humans or would violate any applicable law, ethical principles, or principles of scientific integrity;
- Either we or Novartis may terminate the agreement for a drug by providing written notice to the other party upon the other party's uncured failure to perform a material obligation related to the drug under the agreement, or the entire agreement if the other party becomes insolvent; and
- We may terminate the agreement if Novartis disputes or assists a third party to dispute the validity of any of our patents.

In conjunction with this collaboration, we and Akcea entered into a SPA with Novartis. As part of the SPA, Novartis purchased 1.6 million shares of our common stock for $100 million in the first quarter of 2017. As part of the SPA, Novartis was required to purchase $50 million of Akcea's common stock at the IPO price or our common stock at a premium if an IPO did not occur by April 2018.

To determine the amount of revenue to recognize under our agreements with Novartis, we first concluded that we would account for the collaboration and SPA agreements as a single multiple element arrangement. We next identified four separate units of accounting under the arrangement, each with stand-alone value:

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

We then determined the total consideration under the arrangement was $180.0 million, which included the following:

- $75 million from the upfront payment;
- $100 million from our common stock Novartis purchased under the SPA, including $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 first allocated $71.6 million of the consideration to equity based on the fair value of our common stock Novartis purchased. Next, we allocated the remaining consideration of $108.4 million based on the relative stand-alone selling price of each unit of accounting as follows:

- $64.0 million for the development services for AKCEA-APO(a)-L_{Rx};
- $40.1 million for the development services for AKCEA-APOCIII-L_{Rx};
- $1.5 million for the delivery of AKCEA-APO(a)-L_{Rx} API; and
- $2.8 million for the delivery of AKCEA-APOCIII-L_{Rx} API.

We are recognizing the amount attributed to the development services for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} over the period of time we are performing the services, currently estimated to be through November 2018 and June 2019, respectively. We recognized the amount attributed to the API supply for AKCEA-APOCIII-L_{Rx} when we delivered it to Novartis in 2017. We will recognize the amount attributed to the API supply for AKCEA-APO(a)-L_{Rx} as we deliver it to Novartis. We determined at the inception that all milestones under its Novartis collaboration are substantive milestones and we will recognize any future exercise of an option to license a drug under the Novartis agreement in full in the period the option is exercised. Akcea is responsible for the development activities under this collaboration. As such, Akcea is recognizing the associated revenue in its statement of operations. Akcea pays us sublicense fees for payments that it receives under the collaboration and we recognize those fees as revenue and Akcea recognizes the fees as R&D expense. On a consolidated basis, we eliminate the sublicense fees.

During 2017, we earned revenue of $55.2 million from our relationship with Novartis, which represented 11 percent of our total revenue for 2017. Our balance sheet at December 31, 2017 included deferred revenue of $58.9 million related to our relationship with Novartis.

Roche

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease, or HD, based on our antisense technology. Roche has the option to license the drugs from us through the completion of the first Phase 1 trial. Under the agreement, we are responsible for the discovery and development of an antisense drug targeting huntingtin, or HTT, protein. We evaluated a drug targeting HTT, IONIS-HTT_{Rx}, in a Phase 1/2a clinical study in people with early stage HD.

In December 2017, upon completion of the Phase 1/2a study, Roche exercised its option to license IONIS-HTT_{Rx} and is now responsible for the global development, regulatory and commercialization activities for IONIS-HTT_{Rx}. Under the terms of the agreement, we received an upfront payment of $30 million in April 2013, which we amortized through September 2017. In December 2016, we updated development activities for IONIS-HTT_{Rx} and as a result we are eligible for an additional $3 million payment, which we earned in 2017. We are eligible to receive up to $365 million in a license fee and substantive 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 drug successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on any sales of any product resulting from this alliance. From inception through December 2017, we have received $60 million in milestone payments and upfront fees under this alliance with Roche, not including the $45 million license fee we received in January 2018 for IONIS-HTT_{Rx}, which we recognized into revenue in 2017. We will earn the next milestone payment of $10 million if Roche initiates a Phase 2 trial for IONIS-HTT_{Rx}.

Our alliance with Roche will continue until the earlier of the date Roche's option to obtain the exclusive license under the agreement expires unexercised or, if Roche exercises its option, until the expiration of all payment obligations under the agreement. In addition, the agreement may terminate early under the following situations:

- Roche may terminate the agreement at any time by providing written notice to us; and
- Either we or Roche may terminate the agreement by providing written notice to the other party upon the other party's uncured failure to perform a material obligation under the agreement or if the other party becomes insolvent.

During 2017, 2016 and 2015, we earned revenue of $53.0 million, $7.1 million and $31.2 million, respectively from our relationship with Roche, which represented 10 percent, two percent and 11 percent, respectively, of our total revenue for those years. Our balance sheet at December 31, 2016 included deferred revenue of $1.7 million related to our relationship with Roche.

Satellite Company Partnerships

Achaogen, Inc.

In 2006, we exclusively licensed to Achaogen, Inc. specific know-how, patents and patent applications relating to aminoglycosides. In connection with the license, Achaogen issued to us $1.5 million of Achaogen stock. Achaogen is developing plazomicin, an aminoglycoside Achaogen discovered based on the technology we licensed to Achaogen. If Achaogen successfully develops and commercializes two drugs under our agreement, we will receive payments totaling up to $49.3 million for the achievement of key clinical, regulatory and sales events. The FDA set a Prescription Drug User Fee Act, or PDUFA, date of June 25, 2018 for plazomicin. Achaogen also plans to submit an MAA to the EMA in 2018. From inception through December 2017, we have earned $7 million in milestone payments from Achaogen. We will earn the next milestone payment of $7.5 million if Achaogen obtains regulatory approval for plazomicin in a major market. We are also eligible to receive low single digit royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development, regulatory and commercialization activities of plazomicin.

During 2017, 2016 and 2015, we did not earn any revenue from our relationship with Achaogen.

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into an alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, 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 $5 million technology access fee, participation in fees from Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug Alnylam develops under this alliance, we may receive up to $3.4 million in milestone payments, including up to $1.1 million for the achievement of development milestones and $2.3 million for regulatory milestones. We will earn the next milestone payment of $0.8 million if Alnylam advances a drug in its pipeline. We also have the potential to earn royalties on drug sales and a portion of payments that Alnylam receives from licenses of our technology it grants to its partners, plus royalties. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi, or ssRNAi, therapeutics.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded antisense therapeutics, ssRNAi therapeutics, and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on a nonexclusive basis. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam up to $3.4 million in milestone payments for specified development and regulatory events, plus royalties. To date, we do not have an RNAi-based drug in development.

In 2015, we and Alnylam entered into an alliance in which we formed an intellectual property cross-license under which 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. From inception through December 2017, we have received over $70 million from Alnylam.

During 2017, 2016 and 2015, we earned revenue from our relationship with Alnylam totaling $3.3 million, $1.1 million and $1.3 million, respectively.

Antisense Therapeutics Limited

In 2001, we licensed ATL1102 and ATL1103 to ATL, an Australian company publicly traded on the Australian Stock Exchange. ATL completed a Phase 2a efficacy and safety trial and has also completed a chronic toxicology study in primates to support a potential Phase 2b trial of ATL1102 in people with multiple sclerosis, or MS. In addition, ATL is currently developing ATL1103 for growth and sight disorders. We are eligible to receive royalties on sales of ATL1102 and ATL1103. We may also receive a portion of the fees ATL receives if it licenses ATL1102 or ATL1103. At December 31, 2017 and 2016, we owned less than 10 percent of ATL's equity. During 2017, 2016 and 2015, we did not earn any revenue from our relationship with ATL.

Atlantic Pharmaceuticals Limited

In March 2007, we licensed alicaforsen to Atlantic Pharmaceuticals, a UK-based specialty pharmaceutical company founded in 2006. Atlantic Pharmaceuticals is developing alicaforsen for the treatment of ulcerative colitis, or UC, and other inflammatory diseases. Atlantic Pharmaceuticals is initially developing alicaforsen for pouchitis, a UC indication, followed by UC and other inflammatory diseases. In 2017, under a rolling submission agreement with the FDA, Atlantic Pharmaceuticals filed the nonclinical data package of its NDA for alicaforsen to treat pouchitis. Alicaforsen has also been granted FDA Fast-Track designation, plus U.S. and European Orphan Drug designations for this indication. In exchange for the exclusive, worldwide license to alicaforsen, we received a $2 million upfront payment from Atlantic Pharmaceuticals in the form of equity. Under the agreement, we could receive milestone payments totaling up to $1.4 million for the achievement of regulatory milestones for multiple indications. We will earn the next milestone payment of $0.6 million when Atlantic Pharmaceuticals completes its NDA submission for alicaforsen with the FDA. In 2010, Atlantic Pharmaceuticals began supplying alicaforsen under international named patient supply regulations for people with inflammatory bowel disease, or IBD, for which we receive royalties.

In 2010, 2013 and 2016, we agreed to sell Atlantic Pharmaceuticals alicaforsen drug substance in return for shares of Atlantic Pharmaceuticals' common stock. Additionally, in 2013 we received an advance payment in the form of equity for the initial royalties that we will earn from Atlantic Pharmaceuticals. We recorded a full valuation allowance for all of the equity we received from Atlantic Pharmaceuticals, including the upfront payment, because realization of value from the equity is uncertain. At December 31, 2017 and 2016, we owned approximately 9 percent, respectively, of Atlantic Pharmaceuticals' equity. Because the payments were made in equity, we did not record any revenue. During 2017 and 2016, we did not earn any revenue and during 2015, our revenue was negligible from our relationship with Atlantic Pharmaceuticals.

Dynacure, SAS

In October 2016, we entered into a collaboration with Dynacure to discover, develop and commercialize an antisense drug for the treatment of neuromuscular diseases. We and Dynacure shared research responsibilities and to identify a drug candidate. In November 2017, Dynacure licensed IONIS-DNM2-2.5$_{Rx}$, a drug targeting dynamin 2 for the treatment of centronuclear myopathy, from us. Upon licensing, Dynacure assumed all responsibility for development and commercialization for IONIS-DMN2-2.5$_{Rx}$. Under the terms of the agreement, we obtained a 15 percent equity ownership in Dynacure upon the initiation of the collaboration. We received additional equity and convertible notes in Dynacure for the license of IONIS-DMN2-2.5$_{Rx}$ in 2017. We recorded a full valuation allowance for all of the equity and convertible debt we received from Dynacure, because realization of value from the equity is uncertain. If Dynacure advances a target under this collaboration, we could receive cash or equity up to more than $210 million in a license fee and substantive milestone payments including up to $34.5 million for the achievement of development milestones, up to $111 million for the achievement of regulatory milestones and up to $60 million for the achievement of commercialization milestones. In addition, we are eligible to receive royalties on future product sales of the drug under this collaboration. We will receive additional equity or convertible notes in Dynacure if Dynacure initiates a Phase 1 study for a target under this collaboration. During 2017 and 2016, we did not earn any revenue from our relationship with Dynacure.

Regulus Therapeutics Inc.

In September 2007, we and Alnylam established Regulus as a company focused on the discovery, development and commercialization of microRNA-targeting therapeutics. We and Alnylam retain rights to develop and commercialize, on pre-negotiated terms, microRNA therapeutic products that Regulus decides not to develop either by itself or with a partner. Regulus is addressing therapeutic opportunities that arise from alterations in microRNA expression. Since microRNAs may act as master regulators of the genome, affecting the expression of multiple genes in a disease pathway, microRNA therapeutics define a new platform for drug discovery and development. MicroRNAs may also prove to be an attractive new tool for characterizing diseases. Regulus' focus is on drug discovery and development efforts for diseases with significant unmet medical need in organs to which we have been able to preferentially deliver oligonucleotide therapeutics effectively, such as the liver and kidney. Regulus currently has two drugs in clinical development. In September 2017, Regulus initiated a Phase 2 study of RG-012, a drug to treat people with Alport syndrome. Regulus is studying RGLS4326 in a Phase 1 single ascending dose study designed to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of RGLS4326 administered subcutaneously in healthy volunteers. We are eligible to receive royalties on any future product sales of these drugs.

During 2017, 2016 and 2015, we did not earn any revenue from our relationship with Regulus. During 2015, we sold a portion of our Regulus stock, resulting in a gain of $20.2 million, and proceeds of $25.5 million. During 2016, we sold a portion of our Regulus stock for proceeds of $4.5 million. In January 2017, we sold our remaining investment in Regulus for proceeds of $2.5 million.

Suzhou Ribo Life Science Co., Ltd.

In April 2017, we entered into a collaboration with Ribo to develop and commercialize RNA-targeted therapeutics in China. We licensed IONIS-AR-2.5$_{Rx}$, IONIS-GCGR$_{Rx}$ and IONIS-EZH2-2.5$_{Rx}$ to Ribo under our collaboration to develop and commercialize these drugs in China. In addition, Ribo will be responsible for conducting a multi-year research and drug discovery program to identify drugs that utilize our ssRNAi technology. Following the identification of a development candidate, Ribo may exercise its option to license each drug by paying us a license fee. For each drug that Ribo licenses, Ribo will be responsible for all development and commercialization activities and costs in China. We retained the rights to develop and commercialize ssRNAi technology and all drugs under the collaboration outside of China. Ribo will provide us a royalty-free license to the data and intellectual property created under the collaboration.

Under the agreement, we received an up-front payment of $2 million, which we are amortizing through April 2020. We also obtained approximately nine percent equity ownership in Ribo. We are eligible to receive up to $152.9 million in substantive milestone and other payments, including $13.3 million for the achievement of development milestones and $138.4 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties up to the mid-twenty percent range on sales from any drugs resulting from this collaboration. From inception through December 2017, we have received $2 million in milestone payments and upfront fees under this collaboration with Ribo. We will earn the next milestone payment of $3.3 million if Ribo advances a drug under this collaboration.

During 2017, we earned revenue of $0.7 million from our relationship with Ribo. Our balance sheet at December 31, 2017 included deferred revenue of $1.7 million related to our relationship with Ribo.

The University of Texas MD Anderson Cancer Center

In May 2016, we entered into a collaboration agreement with the University of Texas MD Anderson Cancer Center to identify cancer targets and create novel antisense drugs to treat cancer together. In the collaboration, we and MD Anderson are working together to validate novel "undruggable" cancer targets selected based on human genomic data. We are leading the drug discovery efforts against mutually agreed upon novel targets and MD Anderson is leading development activities through clinical proof of concept. Following clinical proof of concept, we and MD Anderson plan to identify a partner to complete development and to commercialize each drug with us leading business development efforts. Under the five-year collaboration, we and MD Anderson will evenly share costs specific to our collaboration.

External Project Funding

CHDI Foundation, Inc.

Starting in November 2007, CHDI provided financial and scientific support to our Huntington's disease drug discovery program through our development collaboration. In April 2013, we formed an alliance with Roche to develop treatments for Huntington's disease. Under the terms of our agreement with CHDI, we will reimburse CHDI for a portion of its support of our Huntington's disease program out of the payments we receive from Roche. From inception through December 2017, we have made payments of $19.3 million to CHDI, associated with the progression of our Huntington's disease program.

During 2017 and 2016, we did not earn any revenue from our relationship with CHDI. During 2015, our revenue earned from our relationship with CHDI was negligible.

Cystic Fibrosis Foundation

In August 2016, we entered into a collaboration agreement with the Cystic Fibrosis Foundation to discover and advance a drug for the treatment of Cystic Fibrosis. Under this agreement, we received upfront payments of $1 million, which we are amortizing through March 2018. We are eligible to receive additional milestone payments of up to $2 million. Under the agreement, we and the Cystic Fibrosis Foundation will evenly share the first $3 million of costs specific to our collaboration. We will pay the Cystic Fibrosis Foundation up to $18 million in payments upon achieving specific regulatory and sales events if we advance a drug under our collaboration. We will earn the next milestone payment of $0.8 million if we further advance IONIS-ENAC-2.5$_{Rx}$. From inception through December 2017, we have received $2.7 million in milestone payments, upfront fees and other payments under this collaboration, including $1 million we received in 2017 for advancing IONIS-ENAC-2.5$_{Rx}$.

During 2017 and 2016 we earned $1.9 million and $0.6 million, respectively, from our relationship with the Cystic Fibrosis Foundation.

The Ludwig Institute; Center for Neurological Studies

In October 2005, we entered into a collaboration agreement with the Ludwig Institute, the Center for Neurological Studies and researchers from these institutions to discover and develop antisense drugs for amyotrophic lateral sclerosis, or ALS, and other neurological diseases. Under this agreement, we agreed to pay the Ludwig Institute and Center for Neurological Studies modest milestone payments and royalties on any antisense drugs resulting from the collaboration.

In-Licensing Agreements

University of Massachusetts

We have a license agreement with the University of Massachusetts under which we acquired an exclusive license to the University of Massachusetts' patent rights related to SPINRAZA. We paid the University of Massachusetts nominal amounts for license fees and milestone payments we received. We also pay a low single digit royalty on sales of SPINRAZA. During 2017 and 2016, we paid the University of Massachusetts $9.7 million and $0.4 million, respectively. The University of Massachusetts believes we owe them an additional amount pertaining to the license fees and milestones we received. At December 31, 2017, we had an accrued liability of $12.9 million, which reflects our estimate of the additional amount we could pay the University of Massachusetts for the license fees and milestones we received, assuming we reach agreement with the University of Massachusetts regarding the appropriate calculation of these sublicense fees.

Cold Spring Harbor Laboratory

We have a collaboration and license agreement with the Cold Spring Harbor Laboratory under which we acquired an exclusive license to the Cold Spring Harbor Laboratory's patent rights related to SPINRAZA. We paid Cold Spring Harbor Laboratory nominal amounts for license fees and milestone payments we received in 2017 and a low single digit royalty on sales of SPINRAZA. Additionally, we owe a low single digit royalty on future sales of SPINRAZA. During 2017 and 2016, we paid Cold Spring Harbor Laboratory $13.1 million and $3.4 million, respectively.

7. Segment Information and Concentration of Business Risk

We have two reportable segments Ionis Core and Akcea Therapeutics. Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea's stock and consolidated 100 percent of Akcea's results in our financial statements. After Akcea's IPO, we owned approximately 68 percent of Akcea. As a result, beginning in the third quarter of 2017, we began adjusting our financial statements to reflect the noncontrolling interest that we no longer own in Akcea. Our reportable segments remain unchanged as a result of Akcea's IPO. Segment income (loss) from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment we are exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class and/or best-in-class drugs for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy and includes multiple streams of revenue including license fees, milestone payments and royalties, among others.

Akcea is a late-stage biopharmaceutical company focused on developing and commercializing drugs to treat people with serious cardiometabolic diseases caused by lipid disorders.

The following tables show our segment revenue and income (loss) from operations for 2017, 2016 and 2015 (in thousands), respectively.

2017	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 112,540	$ —	$ —	$ 112,540
Licensing and other royalty revenue	9,519	—	—	9,519
Total commercial revenue	122,059	—	—	122,059
R&D revenue under collaborative agreements	384,805	55,209	(54,407)	385,607
Total segment revenue	$ 506,864	$ 55,209	$ (54,407)	$ 507,666
Total operating expenses	$ 373,788	$ 163,871	$ (54,527)	$ 483,132
Income (loss) from operations	$ 133,076	$ (108,662)	$ 120	$ 24,534

2016	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 883	$ —	$ —	$ 883
Licensing and other royalty revenue	19,839	—	—	19,839
Total commercial revenue	20,722	—	—	20,722
R&D revenue under collaborative agreements	338,546	—	(12,648)	325,898
Total segment revenue	$ 359,268	$ —	$ (12,648)	$ 346,620
Total operating expenses	$ 322,192	$ 83,512	$ (12,768)	$ 392,936
Income (loss) from operations	$ 37,076	$ (83,512)	$ 120	$ (46,316)

2015	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
R&D revenue under collaborative agreements	$ 284,015	$ —	$ (2,655)	$ 281,360
Licensing and other royalty revenue	2,343	—	—	2,343
Total segment revenue	$ 286,358	$ —	$ (2,655)	$ 283,703
Total operating expenses	$ 309,492	$ 52,748	$ (2,775)	$ 359,465
Income (loss) from operations	$ (23,134)	$ (52,748)	$ 120	$ (75,762)

The following table shows our total assets by segment at December 31, 2017 and 2016 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
December 31, 2017	$1,341,828	$ 268,804	$ (288,608)	$1,322,024
December 31, 2016	$1,067,770	$ 10,684	$ (165,987)	$ 912,467

We have historically funded our operations from collaborations with corporate partners and a relatively small number of partners have accounted for a significant percentage of our revenue. Revenue from significant partners, which is defined as 10 percent or more of our total revenue, was as follows:

	2017	2016	2015
Partner A	51%	60%	37%
Partner B	14%	2%	33%
Partner C	10%	2%	11%
Partner D	11%	0%	0%
Partner E	3%	19%	2%
Partner F	2%	4%	12%

Contracts receivables at December 31, 2017 and December 31, 2016 were comprised of approximately 84 percent and 92 percent for each year from two significant partners, respectively.

8. Employment Benefits

We have an employee 401(k) salary deferral plan, covering all employees. Employees could make contributions by withholding a percentage of their salary up to the IRS annual limit $18,000 and $24,000 in 2017 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately $3.0 million, $1.7 million and $1.5 million in matching contributions for the years ended December 31, 2017, 2016 and 2015, respectively.

9. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If the potential loss from any legal proceeding is considered probable and the amount can be reasonably estimated, we accrue a liability for the estimated loss. Significant judgment is required to determine the probability of a loss and whether the amount of the loss is reasonably estimable. The outcome of any proceeding is not determinable in advance. As a result, the assessment of a potential liability and the amount of accruals recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding, and may revise our estimates.

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the United States District Court of Northern District of California related to United States Patent Nos. 7,105,499 and 8,481,712, which are jointly owned by Merck Sharp & Dohme Corp. and Ionis Pharmaceuticals, Inc. In the suit Gilead asked the court to determine that Gilead's activities do not infringe any valid claim of the named patents and that the patents are not valid. We and Merck Sharp & Dohme Corp. filed our answer denying Gilead's noninfringement and invalidity contentions, contending that Gilead's commercial sale and offer for sale of sofosbuvir prior to the expiration of the '499 and '712 patents infringes those patents, and requesting monetary damages to compensate for such infringement. In the trial for this case held in March 2016, the jury upheld all ten of the asserted claims of the patents-in-suit. The jury then decided that we and Merck are entitled to four percent of $5 billion in past sales of sofosbuvir. Gilead has stated it would appeal the jury’s finding of validity. In the meantime, Gilead asserted two additional non-jury defenses: waiver and unclean hands. Although the judge rejected the waiver defense, she granted Gilead’s motion claiming that the patents are unenforceable against it under the doctrine of unclean hands. We believe this ruling is contrary to the relevant law and the facts of the case. Accordingly, in July 2016, together with Merck we appealed the decision to the Court of Appeals for the Federal Circuit. Gilead cross-appealed on the issue of validity. Briefing on the appeals is now complete and oral arguments were held in February 2018. Under our agreement with Merck, Merck is responsible for the costs of this suit.

10. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for the years ended December 31, 2017 and 2016 are as follows (in thousands, except per share data).

2017 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 110,304	$ 104,152	$ 120,911	$ 172,299
Operating expenses	$ 96,315	$ 105,823	$ 107,002	$ 173,992
Income (loss) from operations	$ 13,989	$ (1,671)	$ 13,909	$ (1,693)
Net income (loss)	$ 3,468	$ (11,206)	$ (4,896)	$ (4,662)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 3,468	$ (11,206)	$ (976)	$ 2,744
Basic net income (loss) per share (1) (2)	$ 0.03	$ (0.09)	$ 0.00	$ 0.02
Diluted net income (loss) per share (1) (3)	$ 0.03	$ (0.09)	$ 0.00	$ 0.02

2016 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 36,874	$ 38,470	$ 110,927	$ 160,349
Operating expenses	$ 91,526	$ 87,397	$ 94,819	$ 119,194
Income (loss) from operations	$ (54,652)	$ (48,927)	$ 16,108	$ 41,155
Net income (loss)	$ (62,917)	$ (56,855)	$ 7,351	$ 25,865
Basic net income (loss) per share (1)	$ (0.52)	$ (0.47)	$ 0.06	$ 0.21
Diluted net income (loss) per share (1) (4) (5)	$ (0.52)	$ (0.47)	$ 0.06	$ 0.21

(1) We computed net income (loss) per share independently for each of the quarters presented. Therefore, the sum of the quarterly net income (loss) per share will not necessarily equal the total for the year.

(2) As discussed in Note 1, *Organization and Significant Accounting Policies*, we compute basic net income (loss) per share by dividing the total net income (loss) attributable to our common stockholders by our weighted-average number of common shares outstanding during the period. The calculation of total net income (loss) attributable to our common stockholders for the three months ended December 31, 2017 and September 30, 2017 considered our net income for Ionis on a stand-alone basis plus our share of Akcea’s net loss for the periods. To calculate the portion of Akcea’s net loss attributable to our ownership, we multiplied Akcea’s income (loss) per share by the weighted average shares we owned in Akcea during the period.

Our basic net income (loss) per share for the three months ended December 31, 2017, was calculated as follows (in thousands, except per share amounts):

Three Months Ended December 31, 2017	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	45,448	$ (0.35)	$ (15,955)
Akcea's net loss attributable to our ownership			$ (15,955)
Ionis' stand-alone net income			18,672
Net income available to Ionis common stockholders			$ 2,717
Weighted average shares outstanding			124,818
Basic net income per share			$ 0.02

For the three months ended December 31, 2017, 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 those periods. Diluted common equivalent shares for the three months ended December 31, 2017 consisted of the following (in thousands except per share amounts):

Three Months Ended December 31, 2017	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Income available to common shareholders	$ 2,717	124,818	$ 0.02
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,532	
Shares issuable upon restricted stock award issuance	—	507	
Shares issuable related to our ESPP	—	5	
Income available to common shareholders, plus assumed conversions	$ 2,717	126,862	$ 0.02

For the three months ended December 31, 2017, the calculation excluded the 1 percent and 2¾ percent notes because the effect on diluted earnings per share was anti-dilutive.

Prior to Akcea's IPO, we owned Akcea series A convertible preferred stock, which included a six percent cumulative dividend. Upon completion of Akcea's IPO in July 2017, our preferred stock was converted into common stock on a 1:1 basis. The preferred stock dividend was not paid at the IPO because it was not a liquidation event or a change in control. During the three months ended September 30, 2017, Akcea used a two-class method to compute its net income (loss) per share because it had both common and preferred shares outstanding during the periods. The two-class method required Akcea to calculate its net income (loss) per share for each class of stock by dividing total distributable losses applicable to preferred and common stock, including the six percent cumulative dividend contractually due to series A convertible preferred shareholders, by the weighted-average of preferred and common shares outstanding during the requisite period. Since Akcea used the two-class method, accounting rules required us to include our portion of Akcea's net income (loss) per share for both Akcea's common and preferred shares which we owned in our calculation of basic and diluted net income (loss) per share for three months ended September 30, 2017. As a result of this calculation, our total net income (loss) available to Ionis common stockholders for the calculation of net income (loss) per share is different than net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders in the consolidated statements of operations.

Our basic net income (loss) per share for the three months ended September 30, 2017, was calculated as follows (in thousands, except per share amounts):

Three Months Ended September 30, 2017	Weighted Average Shares Owned in Akcea	Akcea's Net Income (Loss) Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	36,556	$ (0.27)	$ (9,870)
Preferred shares	5,651	0.05	283
Akcea's net loss attributable to our ownership			$ (9,587)
Ionis' stand-alone net income			9,168
Net loss available to Ionis common stockholders			$ (419)
Weighted average shares outstanding			124,370
Basic net income per share			$ 0.00

(3) For the three months ended March 31, 2017 we had net income. 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. Diluted common equivalent shares for the three months ended March 31, 2017 consisted of the following (in thousands):

Three Months Ended March 31, 2017	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Income available to common shareholders	$ 3,468	122,861	$ 0.03
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,674	
Shares issuable upon restricted stock award issuance	—	377	
Shares issuable related to our ESPP	—	60	
Income available to common shareholders, plus assumed conversions	$ 3,468	124,972	$ 0.03

For the three months ended March 31, 2017, the calculation excludes the 1 percent and 2¾ percent notes because the effect on diluted earnings per share was anti-dilutive.

(4) For the three months ended December 31, 2016, we had net income. 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. Diluted common equivalent shares for the three months ended December 31, 2016 consisted of the following (in thousands):

Three Months Ended December 31, 2016	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Income available to common shareholders	$ 25,865	121,340	$ 0.21
Effect of diluted securities:			
Shares issuable upon exercise of stock options	—	2,189	
Shares issuable upon restricted stock award issuance	—	403	
Shares issuable related to our ESPP	—	21	
Income available to common shareholders, plus assumed conversions	$ 25,865	123,953	$ 0.21

For the three months ended December 31, 2016, the calculation excludes the 1 percent and 2¾ percent notes because the effect on diluted earnings per share would be anti-dilutive.

(5) For the three months ended September 30, 2016, we had net income. 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. Diluted common equivalent shares for the three months ended September 30, 2016 consisted of the following (in thousands):

Three Months Ended September 30, 2016	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Income available to common shareholders	$ 7,351	120,989	$ 0.06
Effect of diluted securities:			
Shares issuable upon exercise of stock options	—	2,129	
Shares issuable upon restricted stock award issuance	—	202	
Shares issuable related to our ESPP	—	58	
Income available to common shareholders, plus assumed conversions	$ 7,351	123,378	$ 0.06

For the three months ended September 30, 2016, the calculation excludes the 1 percent and 2¾ percent notes because the effect on diluted earnings per share would be anti-dilutive.

Exhibit 3.1

RESTATED CERTIFICATE OF INCORPORATION

OF

ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc., a corporation organized and existing under the General Corporation Law of the State of Delaware, does hereby certify as follows:

FIRST: The name of the corporation is Isis Pharmaceuticals, Inc.

SECOND: The Certificate of Incorporation of the corporation was filed by the Secretary of State on March 25, 1991.

THIRD: The Restated Certificate of Incorporation of the corporation, in the form attached hereto as Exhibit A, has been duly adopted in accordance with the provisions of Section 245 of the General Corporation Law of the State of Delaware by the Board of Directors of the corporation.

FOURTH: Pursuant to Section 245 of the Delaware General Corporation Law, approval of the stockholders of the corporation is not required.

FIFTH: The Restated Certificate of Incorporation so adopted reads in full as set forth in Exhibit A attached hereto and hereby incorporated by reference.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Restated Certificate of Incorporation to be signed by its President and attested to by its Assistant Secretary this 31st day of May, 1991.

ISIS PHARMACEUTICALS, INC.

By _____
Stanley T. Crooke
President

ATTEST:

_____
Aron P. Stern
Assistant Secretary

EXHIBIT A

RESTATED CERTIFICATE OF INCORPORATION
OF
ISIS PHARMACEUTICALS, INC.

I.

The name of the Corporation is Isis Pharmaceuticals, Inc.

II.

The address of the registered office of the Corporation in the State of Delaware is 32 Lookerman Square, Suite L-100, City of Dover, County of Kent, and the name of the registered agent of the Corporation in the State of Delaware at such address is The Prentice-Hall Corporation System, Inc.

III.

The purpose of the Corporation is to engage in any lawful act or activity for which a Corporation may be organized under the General Corporation Law of Delaware.

IV.

(a) The liability of the directors of the Corporation for monetary damages shall be eliminated to the fullest extent permissible under Delaware Law.

(b) The Corporation is authorized to provide indemnification of agents (as defined in Section 145 of the Delaware General Corporation Law) for breach of duty to the Corporation and its stockholders through bylaw provisions, through agreements with the agents, and/or through stockholder resolutions, or otherwise, in excess of the indemnification otherwise permitted by Section 145 of the Delaware General Corporation Law, subject to the limitations on such excess indemnification set forth in Section 102 of the Delaware General Corporation Law.

(c) Any repeal or modification of this Article IV shall be prospective and shall not affect the rights under this Article IV in effect at the time of the alleged occurrence of any act or omission to act giving rise to liability or indemnification.

V.

The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 65,000,000 shares, consisting of 50,000,000 shares of Common Stock, each having a par value of $.001, and 15,000,000 shares of Preferred Stock, each having a par value of $.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

VI.

For the management of the business and for the conduct of the affairs of the Corporation, and in further definition, limitation and regulation of the powers of the Corporation, of its directors and of its stockholders or any class thereof, as the case may be, it is further provided that:

Section 1. Board of Directors.

(a) Management of Corporation. The management of the business and the conduct of the affairs of the Corporation shall be vested in its Board of Directors. The number of directors which shall constitute the whole Board of Directors shall be fixed exclusively by one or more resolutions adopted from time to time by the Board of Directors.

(b) Classified Board. Following the closing of the initial public offering pursuant to an effective registration statement under the Securities Act of 1933, as amended (the "1933 Act"), covering the offer and sale of Common Stock to the public (the "Initial Public Offering"):

(i) Designation of Classes. The directors shall be divided with respect to the time for which they generally hold office into three classes designated as Class I, Class II and Class III. Class I shall consist of two directors, with Class II and Class III consisting of three directors each. At the first annual meeting of stockholders held after the closing of the Initial Public Offering, the term of office of the Class I directors shall expire and Class I directors shall be elected for a full term of three years. At the second annual meeting of stockholders held after the closing of the Initial Public Offering, the term of office of the Class II directors shall expire and Class II directors shall be elected for a full term of three years. At the third annual meeting of stockholders held after the closing of the Initial Public Offering, the term of office of the Class III directors shall expire and Class III directors shall be elected for a full term of three years. At each succeeding annual meeting of stockholders, directors shall be elected for a full term of three years to succeed the directors of the class whose terms expire at such annual meeting.

(ii) Change in Directorships. In case of any increase in the number of directorships, the additional directorships so created shall be classified so that, as nearly as possible, each class shall consist of one third of the number of directors then constituting the whole board. Newly created directorships resulting from any increase in the number of directors shall, unless the Board of Directors determines by resolution that any such newly created directorship shall be filled by the stockholders, be filled only by the affirmative vote of the directors then in office, even though less than a quorum of the Board of Directors. Any director elected in accordance with the preceding sentence shall serve until the next election of the class to which such additional directorship shall have been assigned. Notwithstanding the requirement that the three classes shall be as nearly equal in the number of directorships as possible, no change in the number of directorships shall operate to prevent a director then in office from continuing to serve as such until the expiration of his term or his earlier death, resignation or removal.

(iii) Modification of Section 1(b). Notwithstanding any other provisions of this Certificate of Incorporation (other than the provision for the change in the number of directorships set forth in Section 1(b)(ii)) or any provision of law which might otherwise permit a lesser vote or no vote, but in addition to any affirmative vote of the holders of any particular class or series of the Voting Stock (as defined in Section 1(a) of Article VII) required by law or this Certificate of Incorporation or any Preferred Stock Designation, the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of the Voting Stock, voting together as a single class, shall be required to alter, amend or repeal this Section 1(b).

(c) Removal. Subject to any limitations imposed by law, the Board of Directors or any individual director may be removed from office at any time (i) which cause by the affirmative vote of the holders of at least a majority of the outstanding Voting Stock; or (ii) without cause by the affirmative vote of the holders of at least 66-2/3% of the outstanding Voting Stock.

Section 2. General.

(a) The Board of Directors may from time to time make, amend, supplement or repeal the Bylaws; provided, however, that the stockholders may change or repeal any Bylaw adopted by the Board of Directors by the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of the capital stock of the Corporation (considered for this purpose as one class); and, provided further, that no amendment or supplement to the Bylaws adopted by the Board of Directors shall vary or conflict with any amendment or supplement thus adopted by the stockholders.

(b) The directors of the Corporation need not be elected by written ballot unless the Bylaws so provide.

(c) Following the closing of the Initial Public Offering, no action shall be taken by the stockholders of the Corporation except at an annual or special meeting of the stockholders called in accordance with the Bylaws and no action shall be taken by the stockholders by written consent.

(d) Advance notice of stockholder nominations for the election of directors and of business to be brought by stockholders before any meeting of the stockholders of the Corporation shall be given in the manner provided in the Bylaws of the Corporation.

VII.

Following the closing of the Initial Public Offering:

Section 1. Stockholder Vote Required for Business Combinations.

(a) Stockholder Votes. In addition to any affirmative vote required by law or by this Certificate of Incorporation or by any Preferred Stock Designation, and except as otherwise expressly provided in Section 2 of this Article VII:

(i) any merger or consolidation of the Corporation or any Subsidiary (as hereinafter defined) with (A) any Interested Stockholder (as hereinafter defined) or (B) any other corporation (whether or not itself an Interested Stockholder) which is, or after such merger or consolidation would be, an Affiliate (as hereinafter defined) of an Interested Stockholder; or

(ii) any sale, lease, exchange, mortgage, pledge, transfer or other disposition (in one transaction or a series of transactions) to or with any Interested Stockholder or any Affiliate of any Interested Stockholder of any assets of the Corporation or any Subsidiary having an aggregate Fair Market Value (as hereinafter defined) equal to or greater than 10% of the Corporation’s assets as set forth on the Corporation’s most recent audited consolidated financial statements; or

(iii) the issuance or transfer by the Corporation or any Subsidiary (in one transaction or a series of transactions) of any securities of the Corporation or any Subsidiary to any Interested Stockholder or any Affiliate of any Interested Stockholder in exchange for cash, securities or other property (or a combination thereof) having an aggregate Fair Market Value equal to or greater than 10% of the Corporation’s assets as set forth on the Corporation’s most recent audited consolidated financial statements; or

(iv) the adoption of any plan or proposal for the liquidation or dissolution of the Corporation proposed by or on behalf of any Interested Stockholder or any Affiliate of any Interested Stockholder; or

(v) any reclassification of securities (including any reverse stock split), or recapitalization of the Corporation, or any merger or consolidation of the Corporation with any of its Subsidiaries or any other transaction (whether or not with or into or otherwise involving any Interested Stockholder) which has the effect, directly or indirectly, of increasing the proportionate share of the outstanding shares of any class of equity or convertible securities of the Corporation or any Subsidiary which is Beneficially Owned (as hereinafter defined) by any Interested Stockholder or any Affiliate of any Interested Stockholder;

shall require the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of capital stock of the Corporation entitled to vote generally in the election of directors (the "Voting Stock"), voting together as a single class. Such affirmative vote shall be required notwithstanding any other provisions of this Certificate of Incorporation or any provision of law or of any agreement with any national securities exchange or otherwise which might otherwise permit a lesser vote or no vote.

(b) Definition of Business Combination. The term "Business Combination" as used in this Article VII shall mean any transaction which is referred to in any one or more of subparagraphs (i) through (v) of paragraph (a) of this Section 1.

Section 2. Exceptions to Stockholder Vote Requirement.

The provisions of Section 1 of this Article VII shall not be applicable to any particular Business Combination, and such Business Combination shall require only such affirmative vote as is required by law and any other provision of this Certificate of Incorporation and any Preferred Stock Designation, if, in the case of a Business Combination that does not involve any cash or other consideration being received by the stockholders of the Corporation, solely in their respective capacities as stockholders of the Corporation, the condition specified in the following paragraph (a) is met, or, in the case of any other Business Combination, the conditions specified in either of the following paragraph (a) or paragraph (b) are met:

(a) The Business Combination shall have been approved by a majority of the Continuing Directors (as hereinafter defined); provided however, that this condition shall not be capable of satisfaction unless there are at least two Continuing Directors.

(b) All of the following conditions shall have been met:

(i) The consideration to be received by holders of shares of a particular class (or series) or outstanding capital stock of the Corporation (including Common Stock and other than Excluded Preferred Stock (as hereinafter defined)) shall be in cash or in the same form as the Interested Stockholder or any of its Affiliates has previously paid for shares of such class (or series) of capital stock. If the Interested Stockholder or any of its Affiliates have paid for shares of any class (or series) of capital stock with varying forms of consideration, the form of consideration to be received per share by holders of shares of such class (or series) of capital stock shall be either cash or the form used to acquire the largest number of shares of such class (or series) of capital stock previously acquired by the Interested Stockholder.

(ii) The aggregate amount of (x) the cash and (y) the Fair Market Value, as of the date (the "Consummation Date") of the consummation of the Business Combination, of the consideration other than cash to be received per share by holders of Common Stock in such Business Combination shall be at least equal to the higher of the following (in each case appropriately adjusted in the event of any stock dividend, stock split, combination of shares or similar event):

(A) (if applicable) the highest per share price (including any brokerage commissions, transfer taxes and soliciting dealers' fees) paid by the Interested Stockholder or any of its Affiliates for any shares of Common Stock acquired by them within the two-year period immediately prior to the date of the first public announcement of the proposal of the Business Combination (the "Announcement Date") or in any transaction in which the Interested Stockholder became an Interested Stockholder, whichever is higher, plus interest compounded annually from the first date on which the Interested Stockholder became an Interested Stockholder (the "Determination Date") through the Consummation Date at the publicly announced reference rate of interest of Bank of America, N.T. & S.A. (or such other major bank headquartered in the State of California as may be selected by the Continuing Directors) from time to time in effect in the City of San Francisco less the aggregate amount of any cash dividends paid, and the Fair Market Value of any dividends paid in other than cash, on each share of Common Stock from the Determination Date through the Consummation Date in an amount up to but not exceeding the amount of interest so payable per share of Common Stock; and

(B) the Fair Market Value per share of Common Stock on the Announcement Date or the Determination Date, whichever is higher.

(iii) The aggregate amount of (x) the cash and (y) the Fair Market Value, as of the Consummation Date, of the consideration other than cash to be received per share by holders of shares of any class (or series), other than Common Stock or Excluded Preferred Stock, of outstanding Voting Stock shall be at least equal to the highest of the following (in each case appropriately adjusted in the event of any stock dividend, stock split, combination of shares or similar event), it being intended that the requirements of this paragraph (b)(iii) shall be required to be met with respect to every such class (or series) of outstanding Voting Stock whether or not the Interested Stockholder or any of its Affiliates has previously acquired any shares of a particular class (or series) of Voting Stock):

(A) (if applicable) the highest per share price (including any brokerage commissions, transfer taxes and soliciting dealers' fees) paid by the Interested Stockholder or any of its Affiliates for any shares of such class (or series) of Voting Stock acquired by them within the two-year period immediately prior to the Announcement Date or in any transaction in which it became an Interested Stockholder, whichever is higher, plus interest compounded annually from the Determination Date through the Consummation Date at the publicly announced reference rate of interest of Bank of America, N.T. & S.A. (or such other major bank headquartered in the State of California as may be selected by the Continuing Directors) from time to time in effect in the City of San Francisco less the aggregate amount of any cash dividends paid, and the Fair Market Value of any dividends paid in other than cash, on each share of such class (or series) of Voting Stock from the Determination Date through the Consummation Date in an amount up to but not exceeding the amount of interest so payable per share of such class (or series) of Voting Stock;

(B) the Fair Market Value per share of such class (or series) of Voting Stock on the Announcement Date or on the Determination Date, whichever is higher; and

(C) the highest preferential amount per share, if any, to which the holders of shares of such class (or series) of Voting Stock would be entitled in the event of any voluntary or involuntary liquidation, dissolution or winding up of the corporation.

(iv) After such Interested Stockholder has become an Interested Stockholder and prior to the consummation of such Business Combination: (x) except as approved by a majority of the Continuing Directors, there shall have been no failure to declare and pay at the regular date therefor any full quarterly dividends (whether or not cumulative) on any outstanding Preferred Stock; (y) there shall have been (A) no reduction in the annual rate of dividends paid on the Common Stock (except as necessary to reflect any subdivision of the Common Stock), except as approved by a majority of the Continuing Directors, and (B) an increase in such annual rate of dividends as necessary to reflect any reclassification (including any reverse stock split), recapitalization, reorganization or any similar transaction which has the effect of reducing the number of outstanding shares of the Common Stock, unless the failure so to increase such annual rate is approved by a majority of the Continuing Directors; and (z) neither such Interested Stockholder nor any of its Affiliates shall have become the beneficial owner of any additional shares of Voting Stock except as part of the transaction which results in such Interested Stockholder becoming an Interested Stockholder; provided, however, that no approval by Continuing Directors shall satisfy the requirements of this subparagraph (iv) unless at the time of such approval there are at least two Continuing Directors.

(v) After such Interested Stockholder has become an Interested Stockholder, such Interested Stockholder and any of its Affiliates shall not have received the benefit, directly or indirectly (except proportionately, solely in such Interested Stockholder's or Affiliate's capacity as a stockholder of the Corporation), of any loans, advances, guarantees, pledges or other financial assistance or any tax credits or other tax advantages provided by the Corporation, whether in anticipation of or in connection with such Business Combination or otherwise.

(vi) A proxy or information statement describing the proposed Business Combination and complying with the requirements of the Securities Exchange Act of 1934, as amended (the "1934 Act") and the rules and regulations thereunder (or any subsequent provisions replacing such Act, rules or regulations) shall be mailed to all stockholders of the Corporation at least 30 days prior to the consummation of such Business Combination (whether or not such proxy or information statement is required to be mailed pursuant to such Act or subsequent provisions).

(vii) Such Interested Stockholder shall have supplied the Corporation with such information as shall have been requested pursuant to Section 5 of this Article VII within the time period set forth therein.

Section 3. Definitions.

For the purposes of this Article VII:

(a) A "person" means any individual, limited partnership, general partnership, corporation or other firm or entity.

(b) "Interested Stockholder" means any person (other than the Corporation or any Subsidiary) who or which:

(i) is the Beneficial Owner (as hereinafter defined), directly or indirectly, of 15% or more of the voting power of the then outstanding Voting Stock; or

(ii) is an Affiliate of the Corporation and at any time within the two-year period immediately prior to the date in question was the Beneficial Owner, directly or indirectly, of 15% or more of the voting power of the then outstanding Voting Stock; or

(iii) is an assignee of or has otherwise succeeded to any shares of Voting Stock which were at any time within the two-year period immediately prior to the date in question Beneficially Owned by an Interested Stockholder, if such assignment or succession shall have occurred in the course of a transaction or series of transactions not involving a public offering within the meaning of the 1933 Act.

(c) A person shall be a "Beneficial Owner" of or shall "Beneficially Own" any voting Stock:

(i) which such person or any of its Affiliates or Associates (as hereinafter defined) beneficially owns, directly or indirectly, within the meaning of Rule 13d-3 under the 1934 Act as in effect on March 14, 1988; or

(ii) which such person or any of its Affiliates or Associates has (A) the right to acquire (whether such right is exercisable immediately or only after the passage of time), pursuant to any agreement, arrangement or understanding or upon the exercise of conversion rights, exchange rights, warrants or options, or otherwise, or (B) the right to vote pursuant to any agreement, arrangement or understanding (but shall not be deemed to be the beneficial owner of any shares of Voting Stock solely by reason of a revocable proxy granted for a particular meeting of stockholders, pursuant to a public solicitation of proxies for such meeting, and with respect to which shares neither such person nor any such Affiliate or Associate is otherwise deemed the beneficial owner); or

(iii) which is beneficially owned, directly or indirectly, within the meaning of Rule 13d-3 under the 1934 Act as in effect on the adoption date of this Certificate of Incorporation, by any other person with which such person or any of its Affiliates or Associates has any agreement, arrangement or understanding for the purpose of acquiring, holding, voting (other than solely by reason of a revocable proxy as described in subparagraph (ii) of this paragraph (c)) or disposing of any shares of Voting Stock;

provided, however, that in case of any employee stock ownership or similar plan of the Corporation or of any Subsidiary in which the beneficiaries thereof possess the right to vote any shares of Voting Stock held by such plan, no such plan nor any trustee with respect thereto (nor any Affiliate of such trustee), solely by reason of such capacity of such trustee, shall be deemed, for any purposes hereof, to Beneficially Own any shares of Voting Stock held under any such plan.

(d) For the purposes of determining whether a person is an Interested Stockholder pursuant to paragraph (b) of this Section 3, the number of shares of Voting Stock deemed to be outstanding shall include shares deemed Beneficially Owned through application of paragraph (c) of this Section 3 but shall not include any other unissued shares of Voting Stock which may be issuable pursuant to any agreement, arrangement or understanding, or upon exercise of conversion rights, warrants or options, or otherwise.

(e) “Affiliate” or “Associate” shall have the respective meanings ascribed to such terms in Rule 12b-2 under the 1934 Act as in effect on the adoption date of this Certificate of Incorporation.

(f) “Subsidiary” means any corporation of which a majority of the outstanding shares of any class of equity security is owned, directly or indirectly, by the Corporation; provided, however, that for the purposes of the definition of Interested Stockholder set forth in paragraph (b) of this Section 3, the term “Subsidiary” shall mean only a corporation of which a majority of the outstanding shares of each class of equity security is owned, directly or indirectly, by the Corporation.

(g) “Continuing Director” means a member of the Board of Directors of the Corporation who is originally elected upon the incorporation of the Corporation or who is not an Interested Stockholder or affiliated with an Interested Stockholder or in connection with his or her initial assumption of office is recommended and approved for an appointment or election by a majority of Continuing Directors then on the Board.

(h) “Fair Market Value” means: (i) in the case of stock, the highest closing sale price during the 30-day period immediately preceding the date in question of a share of such stock on the Composite Tape for New York Stock Exchange-Listed Stocks, or, if such stock is not quoted on the Composite Tape, on the New York Stock Exchange, or, if such stock is not listed on such Exchange, on the principal United States securities exchange registered under the 1934 Act on which such stock is listed, or, if such stock is not listed on any such exchange, the highest closing sale price quotation with respect to a share of such stock during the 30-day period preceding the date in question on the National Association of Securities Dealers, Inc. Automated Quotations System or any system then in use, or if no such quotations are available, the fair market value on the date in question of a share of such stock as determined by the Board in accordance with Section 4 of this Article VII; and (ii) in the case of property other than cash or stock, the fair market value of such property on the date in question as determined by the Board in accordance with Section 4 of this Article VII.

(i) In the event of any Business Combination in which the Corporation survives, the phrase “consideration other than cash to be received” as used in paragraphs (b)(ii) and (b)(iii) of Section 2 of this Article VII shall include the shares of Common Stock and/or the shares of any other class (or series) of outstanding Voting Stock retained by the holders of such shares.

(j) “Whole Board” means the total number of directors which this corporation would have if there were no vacancies.

(k) “Excluded Preferred Stock” means any series of Preferred Stock with respect to which the Preferred Stock Designation creating such series expressly provides that the provisions of this Article VII shall not apply.

Section 4. Board Enforcement.

(a) Compliance. A majority of the Whole Board but only if a majority of the Whole Board shall then consist of Continuing Directors or, if a majority of the Whole Board shall not then consist of Continuing Directors, a majority of the then Continuing Directors, shall have the power and duty to determine, on the basis of information known to them after reasonable inquiry, all facts necessary to determine compliance with this Article VII, including, without limitation, (i) whether a person is an Interested Stockholder, (ii) the number of shares of Voting Stock beneficially owned by any person, (iii) whether a person is an Affiliate or Associate of another, (iv) whether the applicable conditions set forth in paragraph (b) of Section 2 have been met with respect to any Business Combination, (v) the Fair Market Value of stock or other property in accordance with paragraph (h) of Section 3, and (vi) whether the assets which are the subject of any Business Combination referred to in paragraph (a)(ii) of Section 1 have or the consideration to be received for the issuance or transfer of securities by the Corporation or any Subsidiary in any Business Combination referred to in paragraph (a)(iii) of Section 1 has, an aggregate Fair Market Value equal to or greater than 10% of the Corporation’s assets as set forth on the Corporation’s most recent audited consolidated financial statements.

(b) Demand as to Interested Stockholder. A majority of the Whole Board shall have the right to demand, but only if a majority of the Whole Board shall then consist of Continuing Directors, or, if a majority of the Whole Board shall not then consist of Continuing Directors, a majority of the then Continuing Directors shall have the right to demand, that any person who it is reasonably believed is an Interested Stockholder (or holds of record shares of Voting Stock Beneficially Owned by any Interested Stockholder) supply this Corporation with complete information as to (i) the record owner(s) of all shares Beneficially Owned by such person who it is reasonably believed is an Interested Stockholder, (ii) the number of, and class or series of, shares Beneficially Owned by such person who it is reasonably believed is an Interested Stockholder and held of record by each such record owner and the number(s) of the stock certificate(s) evidencing such shares, and (iii) any other factual matter relating to the applicability or effect of this Article VII, as may be reasonably requested of such person, and such person shall furnish such information within 10 days after receipt of such demand.

(c) Fiduciary Obligation of Interested Stockholder. Nothing contained in this Article VII shall be construed to relieve any Interested Stockholder from any fiduciary obligation imposed by law.

(d) Modification of Article VII. Notwithstanding any other provisions of this Certificate of Incorporation or any provision of law which might otherwise permit a lesser vote or no vote, but in addition to any affirmative vote of the holders of any particular class or series of the Voting Stock required by law or this Certificate of Incorporation or any Preferred Stock Designation, the affirmative vote of the holders of at least 66-2/3% of the voting power of all of the then outstanding shares of the Voting Stock, voting together as a single class, shall be required to alter, amend or repeal this Article VII.

VIII.

No holder of shares of stock of the Corporation shall have any preemptive or other right, except as such rights are expressly provided by contract, to purchase or subscribe for or receive any shares of any class, or series thereof, of stock of the Corporation, whether now or hereafter authorized, or any warrants, options, bonds, debentures or other securities convertible into, exchangeable for or carrying any right to purchase any share of any class, or series thereof, of stock; but such additional shares of stock and such warrants, options, bonds, debentures or other securities convertible into, exchangeable for or carrying any right to purchase any shares of any class, or series thereof, of stock may be issued or disposed of by the Board of Directors to such persons, and on such terms and for such lawful consideration, as in its discretion it shall deem advisable or as the Corporation shall have by contract agreed.

CERTIFICATE OF DESIGNATION

OF

SERIES C JUNIOR PARTICIPATING PREFERRED STOCK
(Pursuant to Section 151 of the
Delaware General Corporation Law)

ISIS PHARMACEUTICALS, INC., a corporation organized and existing under the General Corporation Law of the State of Delaware (hereinafter called the "Company"), hereby certifies that the following resolution was adopted by the Board of Directors of the Corporation as required by Section 151 of the General Corporation Law at a meeting duly called and held on December 8, 2000:

> RESOLVED, that pursuant to the authority granted to and vested in the Board of Directors of the Company in accordance with the provisions of its Restated Certificate of Incorporation, the Board of Directors hereby creates a series of Preferred Stock, par value $.001 per share, of the Company and hereby states the designation and number of shares, and fixes the relative designations and the powers, preferences and rights, and the qualifications, limitations and restrictions thereof (in addition to the provisions set forth in the Restated Certificate of Incorporation of the Company, which are applicable to the Preferred Stock of all classes and series), as follows:

Series C Junior Participating Preferred Stock:

Section 1. Designation and Amount. One million (1,000,000) shares of Preferred Stock, $.001 par value, are designated "Series C Junior Participating Preferred Stock" with the designations and the powers, preferences and rights, and the qualifications, limitations and restrictions specified herein (the "Junior Preferred Stock"). Such number of shares may be increased or decreased by resolution of the Board of Directors; *provided*, that no decrease shall reduce the number of shares of Junior Preferred Stock to a number less than the number of shares then outstanding plus the number of shares reserved for issuance upon the exercise of outstanding options, rights or warrants or upon the conversion of any outstanding securities issued by the Company convertible into Junior Preferred Stock.

Section 2. Dividends and Distributions.

(A) Subject to the rights of the holders of any shares of any series of Preferred Stock (or any similar stock) ranking prior and superior to the Junior Preferred Stock with respect to dividends, the holders of shares of Junior Preferred Stock, in preference to the holders of Common Stock, par value $.001 per share (the "Common Stock"), of the Company, and of any other junior stock, shall be entitled to receive, when, as and if declared by the Board of Directors out of funds legally available for the purpose, quarterly dividends payable in cash on the first day of April, July, October and January in each year (each such date being referred to herein as a "Quarterly Dividend Payment Date"), commencing on the first Quarterly Dividend Payment Date after the first issuance of a share or fraction of a share of Junior Preferred Stock, in an amount per share (rounded to the nearest cent) equal to the greater of (a) $1.00 or (b) subject to the provision for adjustment hereinafter set forth, 100 times the aggregate per share amount of all cash dividends, and 100 times the aggregate per share amount (payable in kind) of all non-cash dividends or other distributions, other than a dividend payable in shares of Common Stock or a subdivision of the outstanding shares of Common Stock (by reclassification or otherwise), declared on the Common Stock since the immediately preceding Quarterly Dividend Payment Date or, with respect to the first Quarterly Dividend Payment Date, since the first issuance of any share or fraction of a share of Junior Preferred Stock. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the amount to which holders of shares of Junior Preferred Stock were entitled immediately prior to such event under clause (b) of the preceding sentence shall be adjusted by multiplying such amount by a fraction, the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

(B) The Company shall declare a dividend or distribution on the Junior Preferred Stock as provided in paragraph (A) of this Section immediately after it declares a dividend or distribution on the Common Stock (other than a dividend payable in shares of Common Stock); *provided*, that in the event no dividend or distribution shall have been declared on the Common Stock during the period between any Quarterly Dividend Payment Date and the next subsequent Quarterly Dividend Payment Date, a dividend of $1.00 per share on the Junior Preferred Stock shall nevertheless be payable on such subsequent Quarterly Dividend Payment Date.

(C) Dividends shall begin to accrue and be cumulative on outstanding shares of Junior Preferred Stock from the Quarterly Dividend Payment Date next preceding the date of issue of such shares, unless the date of issue of such shares is prior to the record date for the first Quarterly Dividend Payment Date, in which case dividends on such shares shall begin to accrue from the date of issue of such shares, or unless the date of issue is a Quarterly Dividend Payment Date or is a date after the record date for the determination of holders of shares of Junior Preferred Stock entitled to receive a quarterly dividend and before such Quarterly Dividend Payment Date, in either of which events such dividends shall begin to accrue and be cumulative from such Quarterly Dividend Payment Date. Accrued but unpaid dividends shall not bear interest. Dividends paid on the shares of Junior Preferred Stock in an amount less than the total amount of such dividends at the time accrued and payable on such shares shall be allocated pro rata on a share-by-share basis among all such shares at the time outstanding. The Board of Directors may fix a record date for the determination of holders of shares of Junior Preferred Stock entitled to receive payment of a dividend or distribution declared thereon, which record date shall be not more than 60 days prior to the date fixed for the payment thereof.

Section 3. Voting Rights. The holders of shares of Junior Preferred Stock shall have the following voting rights:

(A) Subject to the provision for adjustment hereinafter set forth, each share of Junior Preferred Stock shall entitle the holder thereof to 100 votes on all matters submitted to a vote of the stockholders of the Company. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the number of votes per share to which holders of shares of Junior Preferred Stock were entitled immediately prior to such event shall be adjusted by multiplying such number by a fraction, the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

(B) Except as otherwise provided herein, in any other Certificate of Designation creating a series of Preferred Stock or any similar stock, or by law, the holders of shares of Junior Preferred Stock and the holders of shares of Common Stock and any other capital stock of the Company having general voting rights shall vote together as one class on all matters submitted to a vote of stockholders of the Company.

(C) Except as set forth herein, or as otherwise provided by law, holders of Junior Preferred Stock shall have no special voting rights and their consent shall not be required (except to the extent they are entitled to vote with holders of Common Stock as set forth herein) for taking any corporate action.

Section 4. Certain Restrictions.

(A) Whenever quarterly dividends or other dividends or distributions payable on the Junior Preferred Stock as provided in Section 2 are in arrears, thereafter and until all accrued and unpaid dividends and distributions, whether or not declared, on shares of Junior Preferred Stock outstanding shall have been paid in full, the Company shall not:

(i) declare or pay dividends, or make any other distributions, on any shares of stock ranking junior (either as to dividends or upon liquidation, dissolution or winding up) to the Junior Preferred Stock;

(ii) declare or pay dividends, or make any other distributions, on any shares of stock ranking on a parity (either as to dividends or upon liquidation, dissolution or winding up) with the Junior Preferred Stock, except dividends paid ratably on the Junior Preferred Stock and all such parity stock on which dividends are payable or in arrears in proportion to the total amounts to which the holders of all such shares are then entitled;

(iii) redeem or purchase or otherwise acquire for consideration shares of any stock ranking junior (either as to dividends or upon liquidation, dissolution or winding up) to the Junior Preferred Stock, provided that the Company may at any time redeem, purchase or otherwise acquire shares of any such junior stock in exchange for shares of any stock of the Company ranking junior (either as to dividends or upon dissolution, liquidation or winding up) to the Junior Preferred Stock; or

(iv) redeem or purchase or otherwise acquire for consideration any shares of Junior Preferred Stock, or any shares of stock ranking on a parity (either as to dividends or upon liquidation, dissolution or winding up) with the Junior Preferred Stock, except in accordance with a purchase offer made in writing or by publication (as determined by the Board of Directors) to all holders of such shares upon such terms as the Board of Directors, after consideration of the respective annual dividend rates and other relative rights and preferences of the respective series and classes, shall determine in good faith will result in fair and equitable treatment among the respective series or classes.

(B) The Company shall not permit any subsidiary of the Company to purchase or otherwise acquire for consideration any shares of stock of the Company unless the Company could, under paragraph (A) of this Section 4, purchase or otherwise acquire such shares at such time and in such manner.

Section 5. Reacquired Shares. Any shares of Junior Preferred Stock purchased or otherwise acquired by the Company in any manner whatsoever shall be retired and cancelled promptly after the acquisition thereof. All such shares shall upon their cancellation become authorized but unissued shares of Preferred Stock and may be reissued as part of a new series of Preferred Stock subject to the conditions and restrictions on issuance set forth herein, in the Restated Certificate of Incorporation, or in any other Certificate of Designation creating a series of Preferred Stock or any similar stock or as otherwise required by law.

Section 6. Liquidation, Dissolution or Winding Up. Upon any liquidation, dissolution or winding up of the Company, no distribution shall be made (1) to the holders of shares of stock ranking junior (either as to dividends or upon liquidation, dissolution or winding up) to the Junior Preferred Stock unless, prior thereto, the holders of shares of Junior Preferred Stock shall have received $100 per share, plus an amount equal to accrued and unpaid dividends and distributions thereon, whether or not declared, to the date of such payment, or if greater, the holders of shares of Junior Preferred Stock shall be entitled to receive an aggregate amount per share, subject to the provision for adjustment hereinafter set forth, equal to 100 times the aggregate amount to be distributed per share to holders of shares of Common Stock; or (2) to the holders of shares of stock ranking on a parity (either as to dividends or upon liquidation, dissolution or winding up) with the Junior Preferred Stock, except distributions made ratably on the Junior Preferred Stock and all such parity stock in proportion to the total amounts to which the holders of all such shares are entitled upon such liquidation, dissolution or winding up. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the aggregate amount to which holders of shares of Junior Preferred Stock were entitled immediately prior to such event under the proviso in clause (1) of the preceding sentence shall be adjusted by multiplying such amount by a fraction of the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

Section 7. Consolidation, Merger, Etc. In case the Company shall enter into any consolidation, merger, combination or other transaction in which the shares of Common Stock are exchanged for or changed into other stock or securities, cash and/or any other property, then in any such case each share of Junior Preferred Stock shall at the same time be similarly exchanged or changed into an amount per share, subject to the provision for adjustment hereinafter set forth, equal to 100 times the aggregate amount of stock, securities, cash and/or any other property (payable in kind), as the case may be, into which or for which each share of Common Stock is changed or exchanged. In the event the Company shall at any time declare or pay any dividend on the Common Stock payable in shares of Common Stock, or effect a subdivision or combination or consolidation of the outstanding shares of Common Stock (by reclassification or otherwise than by payment of a dividend in shares of Common Stock) into a greater or lesser number of shares of Common Stock, then in each such case the amount set forth in the preceding sentence with respect to the exchange or change of shares of Junior Preferred Stock shall be adjusted by multiplying such amount by a fraction, the numerator of which is the number of shares of Common Stock outstanding immediately after such event and the denominator of which is the number of shares of Common Stock that were outstanding immediately prior to such event.

Section 8. No Redemption. The shares of Junior Preferred Stock shall not be redeemable.

Section 9. Rank. The Junior Preferred Stock shall rank, with respect to the payment of dividends and the distribution of assets, junior to all series of any other class of the Company's Preferred Stock.

Section 10. Amendment. The Restated Certificate of Incorporation of the Company shall not be amended in any manner which would materially alter or change the powers, preferences or special rights of the Junior Preferred Stock so as to affect them adversely without the affirmative vote of the holders of at least two-thirds of the outstanding shares of Junior Preferred Stock, voting together as a single class.

IN WITNESS WHEREOF, the undersigned have executed this certificate as of December 12, 2000.

By: _____

Print Name: **B. LYNNE PARSHALL**
Executive Vice President,
Chief Financial Officer and Secretary

Exhibit 14.1

IONIS CODE OF ETHICS AND BUSINESS CONDUCT

PHILOSOPHY OF IONIS CODE OF ETHICS AND BUSINESS CONDUCT

Ionis Pharmaceuticals, Inc. (hereinafter referred to as "Ionis" or the "Company") will adhere to high legal and ethical standards. As such, this Code of Ethics and Business Conduct (hereinafter referred to as the "Code of Ethics") applies to each of Ionis' employees (including its executive officers) and each member of the Ionis Board of Directors. This Code of Ethics also applies to all employees and members of the Board of Directors of Ionis' majority-owned subsidiaries. References to Ionis and the Company are references to Ionis and its majority-owned subsidiaries.

COMPLIANCE WITH LAWS AND REGULATIONS

As a U.S. company, Ionis is governed by and required to comply with U.S. federal law. In addition to complying with federal law, Ionis will conduct all its activities in compliance with all applicable national, state and local laws, regulations and judicial decrees wherever it conducts business.

At no time will you take any action on behalf of the Company that you know, or reasonably should know, violates any law or regulation. Whenever possible, you will strive to comply with the spirit of the law as well as its letter.

No code of conduct can cover all circumstances or anticipate every situation. When you encounter situations not addressed specifically by this Code of Ethics, you should apply its overall philosophy and concepts to the situation. You should also refer to specific Company policies on the subject in question or similar subjects. If you still have a question about the appropriateness of an action, you should review the particular circumstances with Ionis' CEO, Chief Compliance Officer or the Audit Committee of the Board of Directors.

ETHICAL CONDUCT

You should strive to act in a manner using good judgment, high ethical standards and honesty in your business dealings on behalf of the Company. Unethical practices and activities do not serve the interests of the Company or the community, even if they do not technically violate the law.

Your Responsibilities

- Know and comply with the Ionis Code of Ethics and Company policies that apply to business activities.
- Be honest, fair and trustworthy in all business activities and relationships.
- Provide and support a culture that values integrity and ethical conduct.
- Avoid all conflicts of interest between work and personal affairs.
- Report suspected violations of law, the Ionis Code of Ethics or Company Policies.
- Cooperate in any investigation into possible violations of law, the Ionis Code of Ethics or Company Policies.

Business Practices

It is Ionis' policy to deal with its business associates, partners, suppliers, competitors and any governments or governmental agencies with which it interacts in an ethical manner. As such, you will comply with the principles outlined below and will take steps to ensure similar compliance by the persons you directly manage.

Product Promotion and Interactions with Healthcare Providers and Organizations

Ionis' commercial subsidiaries will sell medicines in the marketplace.

Strict regulations govern not only our promotional activities but also our educational and commercial relationships with healthcare providers (HCPs) and healthcare organizations (HCOs), including our interactions with physicians, nurses, pharmacists and others who administer, prescribe, purchase or recommend prescription medicines, and organizations that employ HCPs or otherwise provide healthcare services.

All interactions with HCPs and HCOs must be guided by applicable laws, regulations and Ionis' policies, including this Code of Ethics.

The following general principles govern Ionis' interactions with HCPs and HCOs worldwide:

- We will not use any unlawful inducement to sell or to arrange for the recommendation or prescribing of our products;

- We believe that enduring customer relationships are based on integrity and trust. We seek to gain advantage over our competitors through superior products, quality, manufacturing and service, but never through improper business practices;

- Ionis' relationships with HCPs and HCOs are intended to benefit patient care and enhance the practice of medicine. Interactions should not tempt HCPs to place their own personal interests above those of the organizations they represent or the patients who will use or need Ionis' products;

- Ionis will not, directly or indirectly, offer or solicit any improper payment, contribution or other transfer of value for the purpose of obtaining, giving or keeping business.

Promotional activities and materials must always comply with all applicable laws, regulations and codes, and our own marketing and advertising review policies, and must be truthful, accurate, not misleading, consistent with approved product labeling and properly substantiated. Promotional activities and materials must never involve promotion of drugs for off-label indications, uses, doses or populations.

All Ionis personnel involved in product marketing or promotion must familiarize themselves with the applicable standards for interaction with HCPs and all related policies and procedures governing the creation, review, approval and use of promotional materials. Use of unapproved promotional materials is prohibited.

Interaction with Competitors

As a vigorous competitor in the marketplace, Ionis will seek economic knowledge about our competitors. However, you will not engage in illegal or improper acts to acquire any competitor information. In addition, you will not hire competitors' employees for the purpose of obtaining confidential information, urge competitors' personnel, customers or suppliers to disclose confidential information, or seek such information from competitors' employees subsequently hired by the Company.

Bribes, Kickbacks and Similar Payments

You are prohibited from paying or receiving any bribe, kickback or other similar payment to or from any public official, or government, or other individual, to secure any concession, contract or other favorable treatment for Ionis or you. This prohibition extends to the payment or receipt of money or anything else of substantial value when you have reason to believe that some part of the payment or "fee" will be used for a bribe, kickback or other similar activity.

Because Ionis is a global company and does business worldwide, you must comply with the United States Foreign Corrupt Practices Act of 1977. For more detail, please read the "Foreign Corrupt Practices Act," attached as Appendix A.

Books, Records and Information Management

Ionis' books of account and records must be accurately maintained and fully disclose the nature of transactions reflected in them. Penalties for violating the laws and regulations in this area could be severe for the Company and the employees involved. Ionis will maintain these books according to the following record-keeping requirements and in compliance with the spirit and letter of applicable laws and regulations:

- All books, records and accounts must be kept in reasonable detail and must accurately and fairly reflect all transactions and dispositions of the Company's assets.
- All disbursements of funds and all receipts must be properly and promptly recorded.
- No undisclosed or unrecorded fund or account may be established for any purposes.
- False or artificial entries must never be made in any of the books or records of the Company, or in any public record for any reason, nor should the Company's records be falsely altered in any way.

Retention of Records

Legal practice requires the retention of certain records for various periods of time, particularly those relating to taxes, personnel, contracts and corporate structure. When litigation or a government investigation or audit is pending or imminent, you must not destroy any relevant records until the matter is closed. Destruction of records to avoid disclosure in a legal proceeding or investigation may constitute a criminal offense.

Audit Integrity

No officer or director of Ionis, or any other person acting under their direction, will take any action to fraudulently influence, coerce, manipulate, or mislead any independent accountant engaged in the performance of an audit of the Company's financial statements for the purpose of rendering the Company's financial statements materially misleading.

Conflicts of Interest

As an employee you cannot without the Company's express written consent, engage in any employment or business activity other than for the Company. Unless expressly consented to in writing by the Company, your personal activities should not involve the use of Company property, facilities, influence or other resources, and should not reflect discredit upon the Company.

You will not engage in any activity through which you stand to benefit personally from any sale or purchase of goods and services by the Company. This provision does not apply to benefits arising out of your employment with the Company, or to ownership of equity in a publicly traded company which was purchased on the open market and represents (i) less than 1% of such company's outstanding equity and (ii) less than 5% of your equity portfolio.

You must promptly disclose in writing any actual or potential conflicts of interest to Ionis' COO, CEO or Chief Compliance Officer. Ionis will review the matter, as set forth above, and communicate its position in writing.

Pre-Clearance Procedure

All employees must pre-clear any employment or business activity other than for the Company. To do so, you should contact either (i) the CEO, (ii) COO or (iii) Chief Compliance Officerand explain to them the proposed business activity you wish to engage in. If you are an executive officer, the Nominating, Governance and Review Committee will evaluate the proposed business activity and will notify you whether such activity has been approved. For all other employees, the CEO or COO will evaluate the proposed business activity and will notify you whether such activity has been approved. In some cases, the individual(s) reviewing your request may discuss your request with other members of the Ionis management team. Remember, just because you have to pre-clear a certain activity, does not mean that Ionis will prevent you doing it.

Members of the Board of Directors must request and receive a determination of no conflict from the Nominating, Governance and Review Committee before engaging in any activity, including acting as an employee or director for any entity that directly or indirectly competes with Ionis.

Certain Pre-Cleared Business Activities

Ionis' management has already pre-cleared certain business activities that should not cause a conflict of interest. For these activities, employees generally do not need to obtain written permission from the Company. However, please use your common sense because even with pre-cleared activities, conflicts of interest can arise. If you are ever in doubt, you should follow the pre-clearance procedures outlined above. The pre-cleared business activities include:

- Working in the food service or hospitality industry after normal business hours;
- Owning rental property (unless Ionis rents the property);
- Philanthropic or pro bono activities;
- Farming;
- Home-based retail (e.g. Amway, Tupperware, cosmetics), provided you do not solicit sales during Ionis business hours or at the Ionis workplace; and
- Fitness instructor.

Dishonesty and Theft

You will not knowingly:

- Engage in fraud or embezzlement affecting Company property, funds, securities or other assets; or
- Willfully damage or destroy property or materials belonging to the Company, its employees or customers.

In addition, without proper supervisory authorization, you will not knowingly:

- Remove property, material or money from the Company, its employees, or its customers for personal gain, personal use, resale or to give to another party;
- Receive property, materials or money belonging to the Company, its employees or its customers for personal gain, personal use, resale or to give to another party;
- Access, remove, publish, destroy or alter private or confidential information existing in physical Company records or electronically stored information;
- Remove, publish, destroy or alter other physical Company records or electronically stored information affecting the Company, its employees or corporate partners; or
- Copy, reprint, duplicate, or recreate in whole or in part, computer programs or related systems developed or modified by Ionis personnel, or acquired from outside vendors.

Insider Trading

The Company opposes the misuse of material nonpublic information in the trading of securities. You agree that you will at all times adhere to the Company's insider trading policy.

WAIVERS FOR EXECUTIVE OFFICERS AND DIRECTORS

Any waiver of this Code of Ethics for executive officers or members of the Board of Directors must be approved by the Nominating, Governance and Review Committee and must be promptly disclosed to the Company's stockholders, including the reasons for the waiver.

REPORTING SUSPECTED VIOLATIONS

Ionis is committed to complying with all applicable securities laws and to filing fair and accurate disclosures with the SEC. Each Employee who reports suspected accounting improprieties or violations of this Code of Ethics or of any laws specifically including federal mail fraud, wire fraud, or securities fraud statutes will be taken seriously and the allegations will be thoroughly investigated.

An employee who suspects accounting improprieties or violations of this Code of Ethics or of any laws specifically including federal mail fraud, wire fraud, or securities fraud statutes should take the following steps:

1. The employee should immediately communicate his/her concern to the Chief Compliance Officer, the COO or the CEO. To ensure the highest quality response, employees should communicate directly with one of these designated Ionis officials. However, any concern may be made anonymously and will be taken seriously.
2. Any officer receiving such a complaint will immediately communicate the complaint to the Audit Committee or you may directly report a suspected violation to the Chairman of the Audit Committee.
3. The Audit Committee together with management will conduct, if appropriate, a confidential, but not anonymous investigation which will involve talking to the complainant (if known), the accused, and as circumstances warrant, any witnesses, and anyone who may have similar complaints.
4. All parties involved in the investigation will be required to cooperate fully, maintain complete confidentiality and take no action which might be considered retaliatory.
5. Once the investigation is complete, the Audit Committee will make a determination as to what happened, the level of severity and the appropriate remedial action, and will take such action.

Ionis will not discharge, demote, suspend, threaten, harass, or in any other manner discriminate against an employee because you (1) have provided information, caused information to be provided, or otherwise assisted in an investigation regarding any conduct which you reasonably believe constitutes a violation of this Code of Ethics or of the federal mail fraud, wire fraud, or securities fraud statutes, any SEC rule or any provision of federal law relating to fraud against stockholders, when the information or assistance is provided to or the investigation is conducted by a federal regulatory or law enforcement agency, any Member of Congress or Congressional committee, or a person with supervisory authority over the employee or (2) have filed, caused to be filed, testified, participated in or otherwise assisted in a proceeding filed or about to be filed (with any knowledge of Ionis) relating to an alleged violation of the federal mail fraud, wire fraud, or securities fraud statutes, any SEC rule or any provision of federal law relating to fraud against stockholders. An employee who alleges such discharge or discrimination may file a civil complaint with the Secretary of Labor.

CONSEQUENCES OF VIOLATING IONIS' CODE OF ETHICS

If you violate the law, the Ionis Code of Ethics or Ionis' policies, you may be subject to disciplinary action, up to and including termination. If necessary, Ionis may suspend your employment during an investigation into an alleged breach. Additional actions may include reassignment of work duties and limitation in future job opportunities. Ionis may refer violations of law to local or federal law enforcement authorities for possible prosecution.

APPENDIX A – The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act (FCPA) prohibits U.S. companies from making improper payments or gifts to foreign officials. Company policy requires that all directors, officers, employees, agents and consultants of Ionis comply with the FCPA.

Definition of Foreign Official

Under the FCPA, the term “foreign official” includes elected and appointed governmental officials, candidates for public office, foreign political parties, officers and employees of government owned or controlled enterprises, and public international organizations. When in doubt, Ionis employees should consult the Company’s Legal Counsel for advice on whether a potential recipient of a payment is a “foreign official.”

Prohibited Acts

The following acts are prohibited by the FCPA:

1. Authorizing, paying, promising or delivering any payment, gift or favor intended to influence any foreign official on a matter within that person’s responsibilities. For example, any payment to any foreign official for the purposes of obtaining or retaining sales of products or services to Ionis, sales by Ionis of Ionis products or services, to win a bid or contract, or to obtain more favorable tax treatment is prohibited.
2. Any indirect payment to a third party if the payor knows that the third party may make a prohibited payment. For example, any payment to an Ionis agent or consultant where the payor is aware or has a firm belief that such agent or consultant may make an improper payment to a foreign official is prohibited. The Ionis payor may not avoid this prohibition by deliberately ignoring or purposefully avoiding knowledge that a bribe may be paid.
3. Establishing any undisclosed or unrecorded “slush” funds or assets; making any false or artificial entries in company books or records; failing to keep books, records and accounts in reasonable detail to reflect accurately the handling of money and other assets; and failing to maintain internal accounting controls sufficient to verify that no improper payments have been made.

Permissible Payments

The following payments may be made:

1. Payments to a foreign official for the purpose of expediting or securing the performance of a routine governmental action. Payments for the following routine governmental actions are permissible: obtaining permits, licenses or other official documents to qualify to do business in a foreign country; processing governmental papers, such as visas and work orders; assuring police protection, mail pickup and delivery, or scheduling inspections associated with contract performance or inspections related to the transit of goods across country; and providing phone service, power and water supply, loading and unloading cargo or protecting perishable products or commodities from deterioration. Routine governmental action does not include any decision by a foreign official to encourage, to award, to continue or to modify the terms relating to any business with any Ionis entity.

2. Any payment that is lawful under the written laws and regulations of the foreign country.
3. Any reasonable expenditure directly related to the promotion, demonstration or explanation of Ionis products or services or the execution or performance of a contract with a foreign government or agency, such as the travel and lodging expenses of a foreign official on a trip for such purposes.

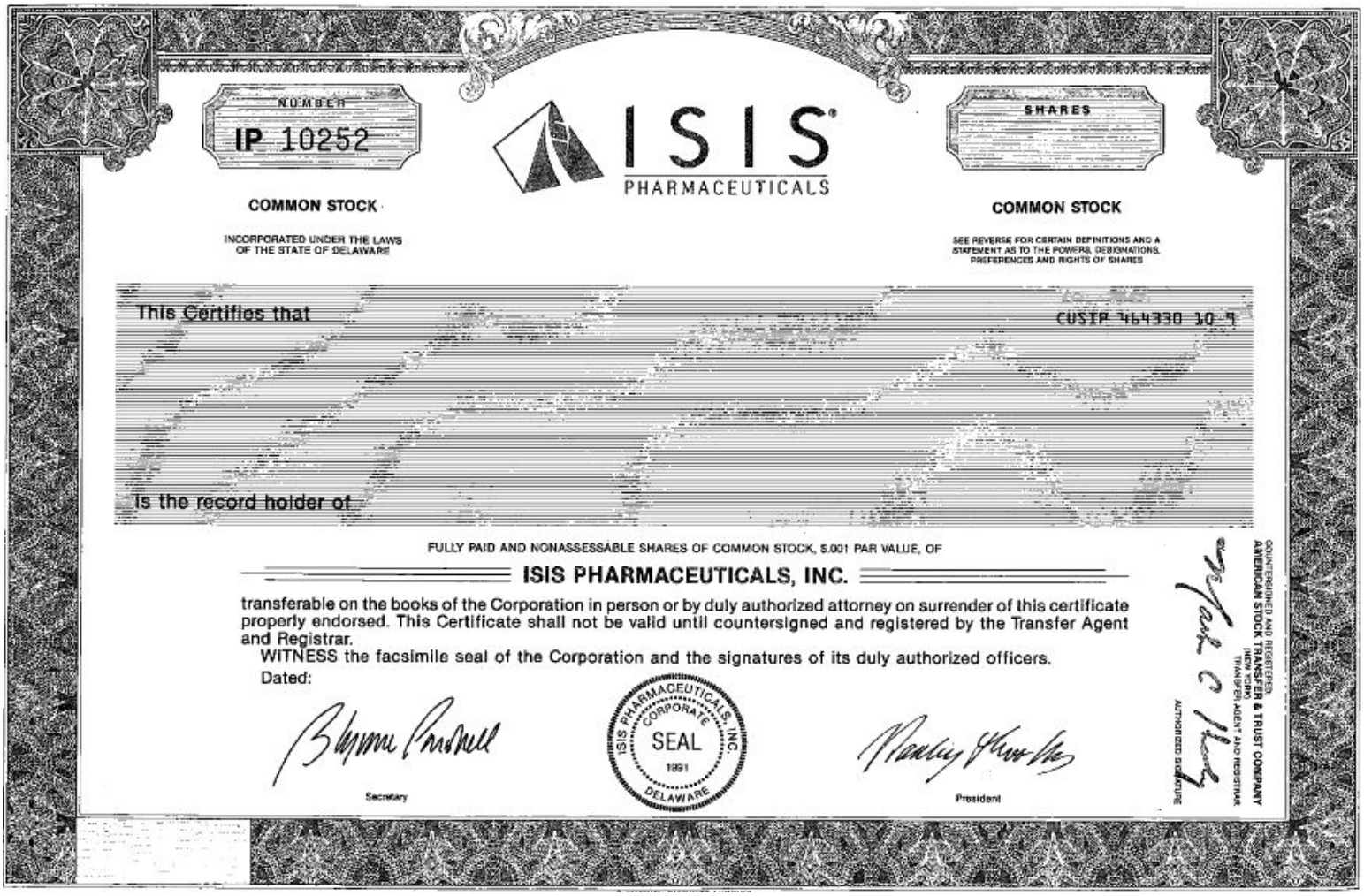
Penalties

Violations of the anti-bribery provisions of the FCPA may result in criminal fines of up to $2,000,000 for corporations and $100,000 and five years imprisonment for individuals. Violations of the accounting provisions may result in fines of up to $2,500,000 for corporations and $1,000,000 and ten years imprisonment for individuals. Under alternative fine provisions, a violator may be fined up to twice the amount of the gain or loss resulting from a violation.

Payments and the FCPA

Neither Ionis nor any director, officer, employee, agent or consultant of the Company will directly or indirectly make or promise illegal payments or contributions, or engage in any other illegal conduct in order to influence customers, suppliers or governmental entities, including their officials or employees, to secure or retain business, to encourage any such employees or officials to fail to perform or to perform improperly their official functions or to influence legislation, nor undertake any of the acts prohibited by the FCPA, as summarized above. Neither Ionis nor any director, officer, employee, agent or consultant of the Company will submit to extortion as a condition of doing business.

Exhibit 4.2



NUMBER
IP 10252

SHARES

ISIS®
PHARMACEUTICALS

COMMON STOCK

INCORPORATED UNDER THE LAWS OF THE STATE OF DELAWARE

COMMON STOCK

SEE REVERSE FOR CERTAIN DEFINITIONS AND A STATEMENT AS TO THE POWERS, DESIGNATIONS, PREFERENCES AND RIGHTS OF SHARES

This Certifies that

CUSIP 464330 10 9

Is the record holder of

FULLY PAID AND NONASSESSABLE SHARES OF COMMON STOCK, $.001 PAR VALUE, OF

ISIS PHARMACEUTICALS, INC.

transferable on the books of the Corporation in person or by duly authorized attorney on surrender of this certificate properly endorsed. This Certificate shall not be valid until countersigned and registered by the Transfer Agent and Registrar.

WITNESS the facsimile seal of the Corporation and the signatures of its duly authorized officers.

Dated:

ISIS PHARMACEUTICALS, INC. CORPORATE SEAL 1991 DELAWARE

Secretary

President

COUNTERSIGNED AND REGISTERED: AMERICAN STOCK TRANSFER & TRUST COMPANY INCORPORATED TRANSFER AGENT AND REGISTRAR

AUTHORIZED SIGNATURE

ISIS PHARMACEUTICALS, INC.

The Corporation is authorized to issue Common Stock and Preferred Stock. The Board of Directors of the Corporation has authority to fix the number of shares and the designation of any series of Preferred Stock and to determine or alter the rights, preferences, privileges, and restrictions granted to or imposed upon any unissued shares of Preferred Stock.

The Corporation will furnish to any stockholder, upon request and without charge, a statement of the powers, designations, preferences and relative, participating, optional or other special rights of each class of stock or series thereof and the qualifications, limitations or restrictions of such preferences and/or rights, so far as the same shall have been fixed, and of the authority of the Board of Directors to designate and fix any preferences, rights and limitations of any wholly unissued series. Any such request should be addressed to the Secretary of the Corporation at its principal office.

The following abbreviations, when used in the inscription on the face of this certificate, shall be construed as though they were written out in full according to applicable laws or regulations:

TEN COM —as tenants in common	**UNIF GIFT MIN ACT—_____Custodian_____**
TEN ENT —as tenants by the entireties	(Cust) (Minor)
JT TEN —as Joint tenants with right of survivorship and not as tenants in common	**under Uniform Gifts to Minors Act_____** (State)

Additional abbreviations may also be used though not In the above list.

For Value Received,_____hereby sell, assign and transfer unto

PLEASE INSERT SOCIAL SECURITY OR OTHER IDENTIFYING NUMBER OF ASSIGNEE

(PLEASE PRINT OR TYPEWRITE NAME AND ADDRESS, INCLUDING ZIP CODE, OF ASSIGNEE)

Shares of the Common Stock represented by the within Certificate, and do hereby irrevocably constitute and appoint

Attorney to transfer the said shares on the books of the within named Corporation with full power of substitution in the premises.

Dated _____

NOTICE: THE SIGNATURE TO THIS ASSIGNMENT MUST CORRESPOND WITH THE NAME AS WRITTEN UPON THE FACE OF THE CERTIFICATE IN EVERY PARTICULAR WITHOUT ALTERATION OR ENLARGEMENT OR ANY CHANGE WHATEVER.

This certificate also evidences and entitles the holder hereof to certain rights as set forth in a Rights Agreement between Isis Pharmaceuticals, Inc, (the "Company") and American Stock Transfer & Trust Company as Rights Agent (the "Rights Agent), dated as of December 8, 2000, as amended from time to time (the "Rights Agreement"), the terms of which are hereby incorporated herein by reference and a copy of which is on file at the principal executive offices of the Company. under certain circumstances, as set forth in the Rights Agreement, such Rights will be evidenced by separate certificates and will no longer be evidenced by this certificate. The Company will mail to the holder of this certificate a copy of the Rights Agreement without charge after receipt of a written request therefor. As described in the Rights Agreement. Rights issued to any Person who becomes an Acquiring Person or an Affiliate or Associate thereof (as defined in the Rights Agreement) and certain related persons, whether currently held by or on behalf of such Person or by any subsequent holder, shall become null and void.

Exhibit 10.4

IONIS PHARMACEUTICALS, INC.

EMPLOYEE CONFIDENTIAL INFORMATION AND INVENTIONS AGREEMENT

In consideration of my employment or continued employment by Ionis Pharmaceuticals, Inc., (the "Company"), and the compensation now and hereafter paid to me, I hereby agree as follows:

1. Recognition of Company's Rights; Nondisclosure. At all times during the term of my employment and thereafter, I will hold in strictest confidence and will not disclose, use, lecture upon or publish any of the Company's Confidential Information (defined below), except as such disclosure, use or publication may be required by the Company in connection with my work for the Company, or unless an officer of the Company expressly authorizes such in writing. I will not make any permitted disclosure, use or publication unless such disclosure, use or publication is in strict compliance with the Company's publication and presentation clearance policy. I will not export, directly or indirectly, any Company products, any direct product thereof, or any related technical data in violation of the United States Department of Commerce's Export Administration Regulations.

The term "Confidential Information" will mean trade secrets, confidential knowledge, data or any other proprietary information of the Company. By way of illustration but not limitation, "Confidential Information" includes (a) inventions, mask works, trade secrets, ideas, processes, formulas, source and object codes, data, programs, other works of authorship, know-how, improvements, discoveries, developments, designs and techniques (hereinafter collectively referred to as "Inventions"); and (b) information regarding plans for research, development, new products, marketing and selling, business plans, budgets and unpublished financial statements, licenses, prices and costs, suppliers and customers; as well as information regarding the skills and compensation of other employees of the Company.

2. Third Party Information. I understand, in addition, that the Company has received and in the future will receive from third parties confidential or proprietary information ("Third Party Information") subject to a duty on the Company's part to maintain the confidentiality of such information and to use it only for certain limited purposes. During the term of my employment and thereafter, I will hold Third Party Information in the strictest confidence and will not disclose (except as required to be disclosed in connection with my work for the Company) Third Party Information unless expressly authorized by an officer of the Company in writing. I will not make any permitted disclosures unless such disclosure is in strict compliance with the Company's publication and presentation clearance policy.

3. Assignment of Inventions

3.1 Assignment

(a) I hereby assign to the Company all my right, title and interest throughout the world 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, trademark or similar statutes (together with the goodwill associated therewith), made or conceived or reduced to practice or learned by me, either alone or jointly with others, during the period of my employment with the Company or within 1 year after termination of my employment, which relate to any Company Invention or to any work performed by me while I was employed by the Company. Inventions assigned to the Company by this Paragraph 3 are hereinafter referred to as "Company Inventions." I agree, upon request, to execute, verify and deliver assignments of such Proprietary Rights to the Company or its designee.

(b) If I am employed by the Company in the State of California, I recognize that this Agreement does not require assignment of any invention which qualifies fully for protection under Section 2870 of the California Labor Code (hereinafter "Section 2870"), which provides as follows:

(i) Any provision in an employment agreement which provides that an employee will assign, or offer to assign, any of his or her rights in an invention to his or her employer will not apply to an invention that the employee developed entirely on his or her own time without using the employer's equipment, supplies, facilities, or trade secret information except for those inventions that either:

(1) Relate at the time of conception or reduction to practice of the invention to the employer's business, or actual or demonstrably anticipated research or development of the employer.

(2) Result from any work performed by the employee for the employer.

(ii) To the extent a provision in an employment agreement purports to require an employee to assign an invention otherwise excluded from being required to be assigned under subdivision (i), the provision is against the public policy of this state and is unenforceable.

3.2 Government. I also agree to assign all my right, title and interest in and to any and all Company Inventions to the United States of America, if such is required to be assigned by a contract between the Company and United States of America or any of its agencies.

3.3 Works for Hire. I acknowledge that all original works of authorship which are made by me (solely or jointly with others) within the scope of my employment as well as those works made by me within 1 year after termination of my employment which relate to any work made by me while I was employed by the Company and which are protectable by copyright are "works made for hire," as that term is defined in the United States Copyright Act (17 U.S.C., Section 101).

4. Enforcement of Proprietary Rights. I will assist the Company in every proper way to obtain and from time to time enforce United States and foreign Proprietary Rights relating to Company Inventions in any and all countries. My obligation to assist the Company with respect to Proprietary Rights relating to such Company Inventions in any and all countries will continue beyond the termination of my employment, but the Company will compensate me at a reasonable rate after my termination for the time actually spent by me if the Company requests such assistance.

I hereby waive and transfer to the Company, any and all claims, of any nature whatsoever, which I now or may hereafter have, for infringement of any Proprietary Rights assigned hereunder to the Company.

5. Obligation to Keep Company Informed. During the period of my employment, I will promptly disclose all Company Inventions to the Company fully and in writing and will hold such Company Inventions in trust for the sole right and benefit of the Company. In addition, after termination of my employment, I will disclose all patent applications filed by me within a year after termination of employment which relate to any Company Invention or to any work performed by me while I was employed by Company.

6. Prior Inventions. Inventions, if any, patented or unpatented, which I made prior to the commencement of my employment with the Company are excluded from the scope of this Agreement. To preclude any possible uncertainty, I have set forth in Exhibit A attached hereto a complete list of all Inventions that I have, alone or jointly with others, conceived, developed or reduced to practice or caused to be conceived, developed or reduced to practice prior to the commencement of my employment with the Company, that I consider to be my property or the property of third parties and that I wish to have excluded from the scope of this Agreement. If disclosure of any such Invention on Exhibit A would cause me to violate any prior confidentiality agreement, I understand that I am not to list such Inventions in Exhibit A but am to inform the Company that all such Inventions have not been listed for that reason.

7. Additional Activities.

(a) I agree that during the period of my employment by the Company I will not, without the Company's express written consent, engage in any employment or business activity other than for the Company. Additionally, during the period of my employment by the Company and for 1 year after the date of termination of my employment with the Company I will not induce any employee of the Company to leave the employ of the Company.

(b) I acknowledge that the Company has developed, through an extensive acquisition process, valuable information regarding actual or prospective partners, licensors, licensees, clients, customers and accounts of the Company ("Trade Secret Information"). I further acknowledge that my use of such Trade Secret Information after the termination of my employment would cause the Company irreparable harm. Therefore, I agree that I will not use 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 the Company.

8. No Improper Use of Materials. During my employment by the Company I will not improperly use or disclose any confidential information or trade secrets, if any, of any former employer or any other person to whom I have an obligation of confidentiality, and I will not bring onto the premises of the Company any unpublished documents or any property belonging to any former employer or any other person to whom I have an obligation of confidentiality unless consented to in writing by that former employer or person.

9. No Conflicting Obligation. I represent that my performance (a) of all the terms of this Agreement and (b) as an employee of the Company, does not and will not breach any agreement to keep in confidence information acquired by me in confidence or in trust prior to my employment by the Company. I have not entered into, and I will not enter into, any agreement that conflicts with this Agreement.

10. Return of Company Documents. When I leave the employ of the Company, I will deliver to the Company any and all laboratory notebooks, conception notebooks, drawings, notes, memoranda, specifications, devices, formulas, molecules, cells, storage media, including software and documents, including any computer printouts, together with all copies thereof, and any other material containing or disclosing any Company Inventions, Third Party Information or Confidential Information of the Company. I further agree that any property situated on the Company's premises and owned by the Company including disks and other storage media, filing cabinets or other work areas, is subject to inspection by Company personnel at any time with or without notice. Prior to leaving, I will cooperate with the Company in completing and signing the Company's termination statement for technical and management personnel.

11. Legal and Equitable Remedies. Because my services are personal and unique and because I may have access to and become acquainted with the Confidential Information of the Company, the Company will have the right to enforce this Agreement and any of its provisions by injunction, specific performance or other equitable relief, without bond, without prejudice to any other rights and remedies that the Company may have for a breach of this Agreement.

12. Notices. Any notices required or permitted hereunder will be given to me at the address specified below or at such other address as I 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 following by another permitted method), telexed, sent by express courier service, or, if sent by certified or registered mail, three days after the date of mailing.

13. General Provisions

13.1 Governing Law. This Agreement will be governed by and construed according to the laws of the State of California.

13.2 Entire Agreement. This Agreement is the final, complete and exclusive agreement of the parties with respect to the subject matter hereof and supersedes and merges all prior discussions between us. No modification or amendment to this Agreement, nor any waiver of any rights under this Agreement, will be effective unless in writing signed by both parties. Any subsequent change or changes in my duties, salary or compensation will not affect the validity or scope of this Agreement. As used in this Agreement, the period of my employment includes any time during which I may be retained by the Company as a consultant.

13.3 Severability. If any of the provisions in this Agreement are deemed unenforceable by law, then the remaining provisions will continue in full force and effect.

13.4 Successors and Assigns. This Agreement will be binding upon my heirs, executors, administrators and other legal representatives and will be for the benefit of the Company, its successors, and its assigns.

13.5 Survival. The provisions of this Agreement will survive the termination of my employment and the assignment of this Agreement by the Company to any successor in interest or other assignee.

13.6 Employment. I agree and understand that nothing in this Agreement will confer any right with respect to continuation of employment by the Company, nor will it interfere in any way with my right or the Company's right to terminate my employment at any time, with or without cause.

13.7 Waiver. No waiver by the Company of any breach of this Agreement will be a waiver of any preceding or succeeding breach. No waiver by the Company of any right under this Agreement will be construed as a waiver of any other right. The Company will not be required to give notice to enforce strict adherence to all terms of this Agreement.

This Agreement will be effective as of the first day of my employment with the Company, namely: _____, 20____.

I UNDERSTAND THAT THIS AGREEMENT AFFECTS MY RIGHTS TO INVENTIONS I MAKE DURING MY EMPLOYMENT, AND RESTRICTS MY RIGHT TO DISCLOSE OR USE THE COMPANY'S CONFIDENTIAL INFORMATION DURING OR SUBSEQUENT TO MY EMPLOYMENT.

I HAVE READ THIS AGREEMENT CAREFULLY AND UNDERSTAND ITS TERMS. I HAVE COMPLETELY FILLED OUT EXHIBIT A TO THIS AGREEMENT.

Dated: _____

_____
Signature

_____
Name of Employee

Address _____

_____

_____

ACCEPTED AND AGREED TO:

Ionis Pharmaceuticals, Inc.

By: _____
Signature

Shannon L. Devers
Printed Name

Vice President, Human Resources
Title

EXHIBIT A

IONIS PHARMACEUTICALS, INC.
2855 Gazelle Court
Carlsbad, California 92010

1. The following is a complete list of all inventions or improvements relevant to the subject matter of my employment by Ionis Pharmaceuticals, Inc. (the "Company") that have been made or conceived or first reduced to practice by me alone or jointly with others prior to my engagement by the Company:

[ ] No inventions or improvements. [ ] See below:

[ ] Due to confidentiality agreements with prior employer, I cannot disclose certain inventions that would otherwise be included on the above-described list.

[ ] Additional sheets attached.

2. I propose to bring to my employment the following devices, materials and documents of a former employer or other person to whom I have an obligation of confidentiality that are not generally available to the public, which materials and documents may be used in my employment pursuant to the express written authorization of my former employer or such other person (a copy of which is attached hereto):

[ ] No material [ ] See below:

[ ] Additional sheets attached.

Date: _____

_____
Employee Signature

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R §§ 200.80(B)4, AND 240.24B-2

EXHIBIT 10.10

AMENDED AND RESTATED
STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT
COLLABORATION, OPTION AND LICENSE AGREEMENT

BETWEEN

IONIS PHARMACEUTICALS, INC.

AND

BIOGEN MA INC.

Table of Contents

AMENDED AND RESTATED STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

This AMENDED AND RESTATED STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 20th day of October, 2017 (the "***Amendment Date***") by and between **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Ionis***"), and **BIOGEN MA INC.**, a Massachusetts corporation, having its principal place of business at 14 Cambridge Center, Cambridge, MA 02142 ("***Biogen***"). Biogen and Ionis 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, Ionis 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, Biogen has expertise in developing and commercializing human therapeutics, and is interested in entering into a strategic relationship with Ionis to explore potential targets for the treatment of neurological and neuromuscular diseases and to create antisense and other drugs to such targets;

WHEREAS, Biogen and Ionis now desire to enter into a new strategic collaboration in neurological and neuromuscular diseases to include (i) a neurological disease research program focused on the identification, validation, and applications of novel targets, (ii) a broad core technology research program focused on enhancing the Parties' knowledge of antisense oligonucleotide pharmacokinetics and pharmacodynamics in the central and peripheral nervous systems, (iii) a targeted drug discovery and development effort, and (iv) the exclusive opportunity for Biogen to select collaboration targets from among all available targets reaching target sanction status in Ionis' neurology program;

WHEREAS, with regard to certain neurology targets Biogen selects as collaboration targets for development using an antisense molecule, Biogen desires Ionis to (i) identify a development candidate for each of the collaboration targets, (ii) develop the development candidate through completion of the first clinical trial designed to demonstrate proof of mechanism or proof of therapeutic benefit, and (iii) provide Biogen an option to obtain an exclusive license under this Agreement to develop, manufacture and commercialize collaboration products in the Field;

WHEREAS, for certain neurology targets relating to ALS and certain other indications, the Parties will collaborate to develop and identify antisense and other drugs to such targets as provided herein;

WHEREAS, Biogen and Ionis are parties to that certain Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement, as amended (the "***Original Agreement***") dated September 5, 2013 (the "***Effective Date***"); and

WHEREAS, Biogen and Ionis seek to amend and restate the Original Agreement in its entirety as set forth herein;

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

ARTICLE 1.
RESEARCH AND DEVELOPMENT

1.1. **Collaboration Overview**.

1.1.1. The intent of the Collaboration is for the Parties to conduct (i) a neurological disease research program focused on the identification, validation, and applications of novel Neurology Targets, (ii) a broad core technology research program focused on enhancing the Parties' knowledge of ASO pharmacokinetics and pharmacodynamics in the central and peripheral nervous systems, and (iii) an expanded drug discovery and development effort in Neurological Disease, including a program specifically focused on certain ALS Targets. This Agreement also provides Biogen the exclusive opportunity to select Collaboration Targets and Biogen Alternate Modality Targets from among all available Neurology Targets Ionis is independently researching up through Target Sanction.

1.1.2. Once a Neurology Target reaches Target Sanction, the Neurology Target may be selected as a Collaboration Target, a Biogen Alternate Modality Target or both under this Agreement. Ionis will generate at least one Development Candidate, if feasible for each Collaboration Program that is not focused on an ALS Target or a Biogen Conducted Non-ALS Target; and advance each such Development Candidate through the completion of the first PoC Trial under the applicable Collaboration Program.

1.1.3. When an ALS Target is selected as a Collaboration Target, Ionis will generate at least one Development Candidate, if feasible, for each ALS Collaboration Program; and Biogen will use Commercially Reasonable Efforts to advance each such Development Candidate through at least the completion of the first PoC Trial under the applicable Collaboration Program.

1.1.4. Once a Biogen Conducted Non-ALS Target reaches Target Sanction, the Biogen Conducted Non-ALS Target may be selected as a Collaboration Target under this Agreement. Ionis will generate at least one Development Candidate, if feasible for each Biogen Conducted Non-ALS Collaboration Program; and Biogen will use Commercially Reasonable Efforts to advance each such Development Candidate through at least the completion of the first PoC Trial under the applicable Collaboration Program.

1.1.5. Ionis will provide Biogen an option to further Develop and ultimately Commercialize (I) Compounds and Collaboration Products under such Collaboration Programs, (II) Biogen Alternate Modality Products or (III) both Collaboration Products and Biogen Alternate Modality Products, in each case, under an exclusive license from Ionis.

1.1.6. The Parties have agreed to form a collaboration steering committee to oversee the Collaboration under this Agreement, a joint research committee reporting to the CSC to oversee the Core Research Program, the Neurological Disease Research Program, and each ASO Development Candidate Identification Plan, and one or more joint development committees reporting to the CSC to oversee the development activities for Development Candidates.

1.1.7. 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. **Research Programs**. Subject to and in accordance with the terms of this Agreement, during the Research Term, Ionis and Biogen will conduct two research programs, each under a separate mutually agreed plan. The first research program will cover research focused on enhancing the Parties' knowledge of ASO pharmacokinetics and pharmacodynamics in the central and peripheral nervous systems (such program, the "***Core Research Program***" and the plan for such program, the "***Core Research Plan***"). The second research program will focus on the identification and validation of High Interest Targets, and the identification of ALS Targets, that are eligible to become Collaboration Targets (such program, the "***Neurological Disease Research Program***" and the plan for such program, the "***Neurological Disease Research Plan***"). Drafts of the Core Research Plan and the initial Neurological Disease Research Plan have been mutually agreed upon by the Parties in writing on or prior to the Effective Date. The Parties will finalize these initially agreed draft plans within [***] days after the Effective Date. Thereafter, the Parties will update such plans at least once before the beginning of each Calendar Year, and submit them to the Neurology JRC for its review and approval. Each update to the Neurological Disease Research Plan will include, at a minimum (i) the activities to support Target Sanction in the Calendar Year covered by such Neurological Disease Research Plan, (ii) any Neurological Disease research to support Collaboration Programs, and (iii) any ongoing work on High Interest Targets from prior Calendar Years. *Notwithstanding the foregoing*, neither Party will be required to complete any activities under the Core Research Plan or Neurological Disease Research Plan if such Party in good faith believes that such activities are not technically feasible given the then-current state of the art.

1.2.1. **Research Term**. The term for the conduct of the Core Research Program and the Neurological Disease Research Program will begin on the Effective Date and will end on the sixth anniversary of the Effective Date (the "***Research Term***"); *provided*, *however*, that (a) with respect to the Neurological Disease Research Program, (i) Ionis will not be required to begin target validation activities under the Neurological Disease Research Program (A) after the [***] anniversary of the Effective Date for any target that is not an ALS Target or (B) after the [***] anniversary of the Effective Date for any ALS Target, in each case, unless otherwise agreed to by the Parties and (ii) if any target validation activities that are Ionis Activities are ongoing under the Neurological Disease Research Plan on such sixth anniversary, Ionis will complete such activities in accordance with the Neurological Disease Research Plan, and the Research Term will be extended until the completion thereof and (b) with respect to the Core Research Program, Ionis will complete all Ionis Activities under the Core Research Plan that are ongoing on such sixth anniversary in accordance with such plan, and the Research Term will be extended until the completion thereof.

1.2.2. **Core Research Program**. The Core Research Program activities will focus primarily on investigating and optimizing delivery of ASOs to the CNS. Ionis will use Commercially Reasonable Efforts to conduct the Ionis Activities under the Core Research Program, and Biogen will use Commercially Reasonable Efforts to conduct the Biogen Activities under the Core Research Program. The Neurology JRC will update the Core Research Plan as needed during the Research Term.

1.2.3. **Neurological Disease Research Program**. The Neurological Disease Research Program activities will focus primarily on identifying and validating novel Neurology Targets and prioritizing a list of High Interest Targets (defined below), including ALS Targets.

(a) ***High Interest Targets***. Under the Neurological Disease Research Plan, Biogen will establish a prioritized list of Neurology Targets, including ALS Targets to designate as high interest targets (each such target, a "***High Interest Target***" and such list the "***High Interest Target List***"). The number of High Interest Targets cannot exceed [***]. The initial High Interest Target List has been mutually agreed upon by the Parties in writing on or prior to the Effective Date. Biogen will present updates, if any, to the High Interest Target List at each meeting of the Neurology JRC. Each Neurology Target added to the High Interest Target List will be a High Interest Target; *provided, however*, that if Ionis notifies Biogen within [***] days after the date on which Ionis receives a High Interest Target List containing a new High Interest Target that (1) [***], (2) such gene target is not eligible to become a High Interest Target hereunder [***], or (3) such gene target is [***], then the applicable gene target will not be a High Interest Target hereunder. When Biogen adds a Neurology Target to the High Interest Target List, Biogen will identify on the High Interest Target List if Biogen intends such target to be an ALS Target. Biogen may convert an ALS Target into a High Interest Target that is not an ALS Target at any meeting of the Neurology JRC. For clarity, Biogen may add any Ionis Neurology Target to the High Interest Target List so long as such Ionis Neurology Target is more than [***] months away from the date on which Ionis in good faith believes [***]. In addition, once target validating activities for a High Interest Target have been initiated under the Neurological Disease Research Plan or by Ionis independently (as presented by Ionis to the Neurology JRC), Biogen may not remove a High Interest Target from the High Interest Target List until [***]. The Parties acknowledge and agree that, as of August 4, 2014, [***] has been designated as a Collaboration Target that is an ALS Target under this Agreement. The Parties further acknowledge and agree that (a) notwithstanding any scientific determination regarding [***], the ALS Collaboration Program for [***] shall be treated as an ALS Collaboration Program that is *not* a [***] Collaboration Program for purposes of this Agreement, (b) [***] is not a Multi-Indication Target (as defined below) and (c) [***] is deemed to be a Pre-Existing Target (as defined below) for purposes of this Agreement.

(b) ***Multi-Indication Targets***. No later than [***] days following the addition of a particular High Interest Target to the High Interest Target List, Ionis may notify Biogen in writing that Ionis believes, in good faith, based upon published scientific literature or the results of Ionis' internal research efforts, that such High Interest Target may have therapeutic benefit beyond Neurological Disease (each such High Interest Target, a "***Multi-Indication Target***", and each such notice a "***Multi-Indication Target Notice***"). The Multi-Indication Target Notice will (i) include materials supporting Ionis' belief that such High Interest Target may have therapeutic benefit beyond Neurological Disease and (ii) specify whether Ionis in good faith believes such Multi-Indication Target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. If within [***] days of its receipt of a Multi-Indication Target Notice Biogen notifies Ionis in writing that Biogen wishes to remove the applicable Multi-Indication Target from the High Interest Target List, then such Multi-Indication Target will not be a High Interest Target but will continue to be a Neurology Target unless and until its status changes by operation of this Agreement. If Biogen does not so notify Ionis that it wishes to remove the applicable Multi-Indication Target from the High Interest Target List within such [***] day period, within [***] days after Biogen's receipt of the applicable Multi-Indication Target Notice, Biogen will notify Ionis whether it agrees with Ionis' determination as to whether the applicable Multi-Indication Target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. If Biogen and Ionis agree with respect to such determination, then the agreed upon designation will be binding upon the Parties with respect to such Multi-Indication Target and the provisions of clauses (b)-(e) of Appendix 3 will apply with respect to such Multi-Indication Target. If Biogen does not agree with such determination, the Multi-Indication Target will be designated as a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target in accordance with Section 1.2.3(d) upon the Neurology JRC agreeing to conduct target validating activities for such Multi-Indication Target under the Neurological Disease Research Plan pursuant to Section 1.2.3(d) and prior to the commencement of such activities. For the avoidance of doubt, if Ionis fails to deliver a Multi-Indication Target Notice within [***] days after the addition of a particular High Interest Target to the High Interest Target List, such High Interest Target will not be a Multi-Indication Target hereunder.

(c) ***Target Validation Under the Neurological Disease Research Program***. The Neurology JRC will agree on an update to the Neurological Disease Research Plan annually. The first [***] years of the Research Term are planned to focus on validating the role of novel Neurology Targets that are not ALS Targets in Neurological Disease, with the goal of achieving Target Sanction for High Interest Targets, and providing for all pre-clinical development work under the Neurological Disease Research Plan required to validate such High Interest Targets. Biogen will have final decision-making authority with respect to [***]. The Neurology JRC will determine the number of High Interest Targets for which activities to support Target Sanction will be conducted during each Calendar Year of the Research Term, which number will reflect the number of targets the Neurology JRC determines that Ionis can, in the exercise of Commercially Reasonable Efforts, (i) [***], (ii) [***], (iii) [***], and taking into account resources that may be used for ALS Targets, in each case using the number of FTEs provided for under Section 1.11. Prior to the initiation of any activities to support Target Sanction with respect to any High Interest Target, Biogen will notify Ionis if such High Interest Target is a Neurology Target with respect to which Biogen has [***] intended for a neurology indication (a ***"Pre-Existing Target"***). Ionis will use Commercially Reasonable Efforts to conduct such activities to support Target Sanction on such High Interest Targets each year during the Research Term. The Neurological Disease Research Plan will identify which Party will be responsible for the activities related to validation of such targets. It is anticipated that Biogen will perform the [***] required under the Neurological Disease Research Plan where Biogen, at such time, already has in place at Biogen or through its collaborators the appropriate [***] and the ability to conduct such [***]; and that all other such [***] will be conducted by Ionis. Each Party will be responsible for the cost of the work it conducts under the Neurological Disease Research Program as more specifically detailed in Section 1.12 and Section 1.13. Neither Party will be required to conduct work using [***] that are not similar in cost or technical feasibility to the [***] such Party has obtained from Third Parties and uses for its other programs.

(d) ***Target Validation for Multi-Indication Targets*****.** If the Neurology JRC agrees to conduct target validating activities under the Neurological Disease Research Plan with respect to any Multi-Indication Target that the Parties did not agree to designate as a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target pursuant to Section 1.2.3(b), within [***] days after such agreement, the CSC will meet to determine whether such target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. If the CSC agrees on the appropriate classification for such Multi-Indication Target, the provisions of clauses (b)-(e) of APPENDIX 3 will apply with respect to such Multi-Indication Target. If the CSC cannot unanimously agree on the appropriate classification for a Multi-Indication Target at the applicable meeting, then such classification will be made pursuant to clause (a) of APPENDIX 3.

(e) ***Neurology Targets that are not High Interest Targets***. Subject to the provisions of Section 1.4 and Section 2.1.1(b) below, during the Research Term, either Party may work outside of the Collaboration on any Neurology Target that is not (i) a High Interest Target for which target validating activities are planned under the then-current Neurological Disease Research Plan, (ii) a Collaboration Target, or (iii) a Biogen Alternate Modality Target.

1.2.4. ***Provision of ASOs for Research Outside of the Neurological Disease Research Program***. During the Research Term, in accordance with and subject to the terms and conditions set forth on SCHEDULE 1.2.4 (which represent the non-financial terms upon which Ionis generally provides its partners on a non-exclusive basis, research ASOs for independent research), Biogen may ask Ionis to use its ASO technology to provide research ASOs for up to [***] gene targets each successive [***] month period that are the focus of Biogen programs that are not part of the Collaboration.

1.3. **Process for Designating High Interest Targets as Collaboration Targets or Biogen Alternate Modality Targets**. After the Parties complete the activities to achieve Target Sanction for a particular High Interest Target that is not an ALS Target, Ionis will deliver a Target Sanction Data Package for such High Interest Target to the Neurology JRC for review as soon as reasonably practicable. Each time Ionis delivers the Neurology JRC a Target Sanction Data Package for a High Interest Target under this Section 1.3 the Parties will schedule a meeting of the Neurology JRC within [***] days following delivery of such Target Sanction Data Package. At such meetings the Neurology JRC will determine and record in the Neurology JRC minutes whether an ASO or Alternate Modality is the best therapeutic approach to pursue for such High Interest Target. If the Neurology JRC cannot unanimously agree on which modality is the best therapeutic approach to pursue for a particular High Interest Target at such meeting, Biogen will have final decision making authority on the matter. Within the later of (x) [***] days following such meeting of the Neurology JRC or (y) [***] days after Biogen's receipt of the Target Sanction Data Package for such High Interest Target, by written notice to Ionis, Biogen will either designate such High Interest Target as a Collaboration Target (in which case Section 1.6 will apply), a Biogen Alternate Modality Target (in which case Section 1.7 will apply), or a Deferred Target (in which case Section 1.8 will apply). If Biogen does not designate such High Interest Target as a Collaboration Target, a Biogen Alternate Modality Target, or Deferred Target within the timeframe set forth in the previous sentence, then (A) such High Interest Target (I) will not be designated a Collaboration Target or Biogen Alternate Modality Target and (II) will no longer be a Neurology Target under this Agreement and (B) the provisions of Section 2.1.1(f) will apply with respect to such target. Notwithstanding the foregoing, if Ionis delivers the Neurology JRC a Target Sanction Data Package for a High Interest Target under this Section 1.3 and such High Interest Target is a Pre-Existing Target, then the Neurology JRC will not meet to discuss which modality is the best therapeutic approach for such High Interest Target, but Biogen will have [***] days after receipt of such Target Sanction Data Package to designate such High Interest Target as a Collaboration Target or a Deferred Target (treating, for purposes of Section 1.8, such target as a High Interest Target for which the best therapeutic modality was determined to be an ASO) by written notice to Ionis, but will not have the right to designate such High Interest Target as a Biogen Alternate Modality Target. If Biogen does not designate such High Interest Target as a Collaboration Target or Deferred Target within the timeframe set forth in the previous sentence, then (X) such High Interest Target (I) will not be designated a Collaboration Target or a Deferred Target and (II) will no longer be a Neurology Target under this Agreement and (Y) the provisions of clause (x) (but not clause (y)) of Section 2.1.1(f) will apply with respect to such target.

1.4. **Process for Designating Ionis Neurology Targets as Collaboration Targets**. If, during the Research Term in the course of conducting work outside of the Collaboration with respect to any Ionis Neurology Target, Ionis achieves Target Sanction with respect to such Ionis Neurology Target, then Ionis will deliver a Target Sanction Data Package for such Ionis Neurology Target to the Neurology JRC for review as soon as reasonably practicable. Within [***] days after the date Ionis delivered the applicable Target Sanction Data Package to the Neurology JRC, by written notice to Ionis, Biogen will either designate such Ionis Neurology Target as a Collaboration Target (in which case Section 1.6 will apply), or, to the extent permitted below, a Biogen Alternate Modality Target (in which case Section 1.7 will apply). If such Ionis Neurology Target was not a High Interest Target on the date of Target Sanction, Biogen will only have the right to designate such target as a Collaboration Target (and not, for the avoidance of doubt, as a Biogen Alternate Modality Target). If Biogen does not designate such Ionis Neurology Target as a Collaboration Target, or a Biogen Alternate Modality Target within [***] days after the date Ionis delivered the applicable Target Sanction Data Package to the Neurology JRC, such Ionis Neurology Target will no longer be a Neurology Target under this Agreement and Ionis and its Affiliates may work independently or with any Third Party with respect to the discovery, research, development, and commercialization of ASOs (or any other compounds) targeting such Ionis Neurology Target.

1.5. **Process for Designating ALS Targets as Collaboration Targets**. If Biogen desires Ionis to initiate ASO drug discovery activities on a particular ALS Target, then at the same time the Neurological Disease Research Plan for the Calendar Year in which Biogen desires Ionis to initiate such activities is updated to include activities for such Calendar Year, Biogen will designate such ALS Target as a Collaboration Target by providing written notice to Ionis; *provided*, if such ALS Target is a Multi-Indication Target, Biogen cannot designate such ALS Target as a Collaboration Target until such target has been classified by the CSC or by operation of APPENDIX 3 as a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target. In addition, Biogen cannot designate more than [***] ALS Targets as Collaboration Targets in any successive [***]-month period, and the total number of ALS Targets that are Collaboration Targets cannot exceed [***] without the Parties' mutual agreement.

1.6. Consequences of Designating Collaboration Targets.

1.6.1. Subject to and in accordance with the terms of this Agreement, for each Collaboration Target designated under Section 1.3, Section 1.4, Section 1.5, Section 1.8, Section 3.2.1, or Section 3.2.4.1, Ionis and Biogen will be responsible for conducting collaboration programs in accordance with this Agreement to discover, Develop and Manufacture Collaboration Products and, upon Biogen's exercise of the applicable Option, Biogen will be responsible for Commercializing Collaboration Products (each, a "***Collaboration Program***"). For each Collaboration Target, an ASO Development Candidate Identification Plan and Initial Development Plan will be established pursuant to Section 1.10.1 and Section 1.10.2(d), respectively. For each Collaboration Program, Ionis will use its Commercially Reasonable Efforts to (i) conduct drug discovery activities, according to the applicable ASO Development Candidate Identification Plan to identify a Development Candidate for the applicable Collaboration Target, and (ii) for each Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, conduct drug development activities for each Development Candidate through completion of the first PoC Trial in accordance with the applicable Initial Development Plan; *provided* that, in each case unless the Neurology JRC unanimously agrees under Section 1.11 to re-allocate resources to support additional Collaboration Programs and, except for any activities Ionis conducts for Collaboration Targets designated under that certain side letter between the Parties, dated as of October 28, 2016 (the "***ALS Letter Agreement***") attached hereto as SCHEDULE 1.6.1, Ionis will not be required to commence work on more than [***] Collaboration Programs in any rolling [***] month period; *provided, further*, that, if Biogen has designated more than [***] High Interest Targets as Collaboration Targets pursuant to Section 1.3 in any rolling [***] month period, such excess targets will be treated the same as "*Deferred Targets*" hereunder until the earlier of (a) such time as Ionis has agreed to commence work on such excess targets, (b) such time as Ionis is otherwise obligated to commence such work hereunder because Ionis has commenced work on fewer than [***] targets in a rolling [***] month period and (c) the expiration of the Research Term and, notwithstanding the provisions of Section 6.2.1, Biogen will not be obligated to make the payment under Section 6.2.1 with respect to such target until such time. For each ALS Collaboration Program and each Biogen Conducted Non-ALS Collaboration Program, Biogen will use its Commercially Reasonable Efforts to conduct drug development activities for each Development Candidate through completion of the [***] in accordance with the applicable Initial Development Plan.

1.6.2. *Notwithstanding the foregoing*, if the applicable Collaboration Target is an Equal Multi-Indication Target, the Parties will not conduct any activities under this Section 1.6 unless and until Ionis and Biogen have agreed on a development plan and enhanced economic provisions to be paid by Biogen for the Non-Neurological Indications pursuant to clause (c) of APPENDIX 3.

1.7. **Consequences of Designating Biogen Alternate Modality Targets**. If Biogen designates a particular Neurology Target as a Biogen Alternate Modality Target under this Agreement (including Section 1.3, Section 1.4, Section 1.8, Section 3.2.2 or Section 3.2.4.2), Biogen will pay Ionis the milestone payment under Section 6.2.2 within 45 days of the designation of such Biogen Alternate Modality Target, *provided*, *however*, if Biogen determines that an HSR Filing is required to be made under the HSR Act for Biogen to receive the license under Section 4.1.1(b) with respect to such Biogen Alternate Modality Target and notifies Ionis of such determination within five days after the designation of such Biogen Alternate Modality Target, the Parties will promptly file an HSR Filing in accordance with Section 3.1.4 and the due date for Biogen to pay Ionis the milestone payment under Section 6.2.2 will be extended until 5:00 pm (Eastern Time) on the [***] Business Day after the HSR Clearance Date.

1.8. **Deferring the Selection of a Collaboration Target or Biogen Alternate Modality Target**.

1.8.1. ***Right to Defer***. If under Section 1.3 Biogen provides Ionis a notice (each, a "***Deferral Notice***") electing to defer selecting a High Interest Target as a Collaboration Target or a Biogen Alternate Modality Target (each, a "***Deferred Target***"), and there is at least [***] at the time of Deferral Notice, then Biogen may defer selecting such High Interest Target as a Collaboration Target or a Biogen Alternate Modality Target for a period of up to the shorter of (i) (A) with respect to any High Interest Target for which the best therapeutic modality was determined to be an ASO, [***] or (B) with respect to any High Interest Target for which the best therapeutic modality was determined to be an Alternate Modality, [***], or (ii) the end of the Research Term (the "***Deferral Period***"); *provided, however,* Biogen may only defer up to [***] High Interest Targets under this Section 1.8.1 at any given time. For the avoidance of doubt, the limitation in the preceding proviso will not apply with respect to any Collaboration Target that is treated the same as a Deferred Target pursuant to Section 1.6.1.

1.8.2. ***Deferral Fee***. For each High Interest Target Biogen elects to defer under this Section 1.8, Biogen will pay Ionis an annual deferral fee of (a) $[***] for each such Deferred Target for which the best therapeutic approach is determined to be an ASO or (b) $[***] for each such Deferred Target for which the best therapeutic approach is determined to be an Alternate Modality, in each case, in accordance with Section 1.3. No deferral fee will be due under this Section 1.8.2 with respect to any Collaboration Target that is treated the same as a Deferred Target pursuant to Section 1.6.1. Each annual deferral fee for a Deferred Target will be paid in advance for the ensuing [***] month period, with the initial annual deferral fee for all Deferred Targets due within [***] days after the date Biogen delivers the applicable Deferral Notice to Ionis, and each annual deferral fee due thereafter during the Deferral Period on the anniversary of the date Biogen delivered such Deferral Notice. If any such annual deferral fee is due after the date that is [***] year prior to the expiration of the Research Term, such deferral fee will be pro-rated to account for the number of days remaining in the Research Term (where such pro-ration will be based on the number of days between the due date for such deferral fee and the end of the Research Term, divided by 365).

1.8.3. ***Designating a Deferred Target as a Collaboration Target or Biogen Alternate Modality Target; Credit for Deferral Fees***. Biogen may designate a Deferred Target as a Collaboration Target or Biogen Alternate Modality Target, as applicable, by delivering written notice to Ionis of such designation (and if a Biogen Alternate Modality Target, the milestone payment under Section 6.2.2), before the expiration of the applicable Deferral Period under this Section 1.8; *provided, however*, that Biogen will not be permitted to designate such Deferred Target as a Biogen Alternate Modality Target if such Deferred Target is a Pre-Existing Target. Biogen may credit [***]% of the total amount paid to Ionis under Section 1.8.2 for such Deferred Target against the milestone payment under Section 6.2.1 or Section 6.2.2, as applicable, for such Deferred Target. If Biogen does not designate a Deferred Target as a Collaboration Target or Biogen Alternate Modality Target in accordance with this Section 1.8.3 before the expiration of the applicable Deferral Period, then such gene target will no longer be a Neurology Target under this Agreement and any payments made by Biogen under this Section 1.8 for such Deferred Target will be non-creditable and non-refundable.

1.8.4. **Accelerating the Deferral Period with a Deferred Target Development Candidate**.

(a) Ionis and its Affiliates may, for its own benefit and not for the benefit of any Third Party, conduct drug discovery activities to identify a Development Candidate for any Deferred Target for which the best therapeutic modality was determined to be an ASO (such Development Candidate, a "***Deferred Target Development Candidate***"); *provided* that Ionis may not use the FTEs provided for under Section 1.11 to conduct such activities. Ionis will notify the Neurology JRC of any such activities and keep the Neurology JRC reasonably apprised of the status thereof at each meeting of the Neurology JRC. If Ionis designates a Deferred Target Development Candidate targeting a particular Deferred Target (such target, an "***Accelerated Target***"), Ionis may notify Biogen in writing regarding Ionis' designation of such Deferred Target Development Candidate and will provide Biogen the applicable Development Candidate Data Package. Within [***] days following Biogen's receipt of the applicable Development Candidate Data Package, Biogen may designate the Accelerated Target as a Collaboration Target; *provided however*, that if Biogen designates such Accelerated Target as a Collaboration Target, in addition to any credits for annual deferral fees under Section 1.8.3, Biogen may credit a pro-rated portion of the un-credited [***]% of the last annual deferral fee paid to Ionis under Section 1.8.2 for such Deferred Target towards the applicable milestone payment under Section 6.2.1 (where such pro-ration will be based on the number of days between the payment of such deferral fee and the applicable designation of such Accelerated Target as a Collaboration Target, divided by the lesser of 365 days and the number of days between the payment of such deferral fee and the end of the Research Term).

(b) If Biogen does not, within such [***] day period, designate the Accelerated Target as a Collaboration Target under this Section 1.8.4, then, such Accelerated Target will no longer be a Neurology Target and Ionis and its Affiliates may work independently or with any Third Party with respect to the discovery, research, development, and commercialization of ASOs (or any other compounds) targeting such Accelerated Target; *provided however* that if prior to the end of the Deferral Period originally applicable to such Accelerated Target, Ionis or any of its Affiliates enters into an agreement with a Third Party pursuant to which Ionis or its Affiliate grants such Third Party a license to develop or commercialize such Deferred Target Development Candidate, Ionis will pay to Biogen [***]% of any amounts (other than Excluded Payments) received by Ionis or its Affiliate under such agreement with such Third Party until such time as Ionis has reimbursed Biogen for [***]% of the last annual deferral fee paid to Ionis under Section 1.8.2 for such Deferred Target.

1.9. **End of Research Term**. At the end of the Research Term, (i) neither Ionis nor Biogen will have an obligation to perform any activities under the Core Research Program or the Neurological Disease Research Program; (ii) the High Interest Target List (including the ALS Targets) will be dissolved, and any Neurology Targets that have not been designated Collaboration Targets or Biogen Alternate Modality Targets will no longer be Neurology Targets under this Agreement; (iii) Ionis' obligations and Biogen's rights under this Agreement with respect to such Neurology Targets and any ASOs targeting such Neurology Targets will then terminate; and (iv) at Ionis' request, Biogen will provide to Ionis any data generated under the Core Research Program and the Neurological Disease Research Program and licensed to Ionis under Section 4.3.2. For clarity, the expiration of the Research Term will not affect Biogen's rights or Ionis' obligations with respect to Collaboration Programs or Biogen Alternate Modality Programs under this Agreement, including, in the case of Collaboration Programs, Ionis' obligation under Section 1.10.1 to use Commercially Reasonable Efforts to identify a Development Candidate for each applicable Collaboration Program.

1.10. **Ionis' Research and Development Responsibilities**.

1.10.1. **Development Candidate Identification**.

(a) **ASO Development Candidate Identification Plans**. For each Collaboration Program, within [***] days after the designation of the applicable Collaboration Target, Ionis will provide the Neurology JRC an initial draft plan to identify a Development Candidate under the applicable Collaboration Program, (such plan, as may be modified from time to time to address the discovery, research and optimization activities Ionis will conduct under the applicable Collaboration Program an "***ASO Development Candidate Identification Plan***"). The Neurology JRC will review such plan and agree on a final ASO Development Candidate Identification Plan for such Collaboration Program, which plan will be generally consistent with Ionis' other plans for other gene targets. Ionis will carry out its drug discovery efforts for each Collaboration Program pursuant to the applicable ASO Development Candidate Identification Plan in a manner consistent with its internal practices for other gene targets with the goal of identifying a Development Candidate for the applicable Collaboration Program as soon as practicable; *provided* that Ionis will not start work on any Equal Multi-Indication Target unless and until Ionis and Biogen have agreed on a development plan and enhanced economic provisions to be paid by Biogen for Non-Neurological Indications in accordance with APPENDIX 3. Ionis will update each ASO Development Candidate Identification Plan as needed and submit it to the Neurology JRC for its review and approval. For each Collaboration Program, Biogen will pay Ionis the milestone payment set forth in Section 6.2.1 following receipt of the applicable Design Notice.

(b) **Biomarker Work**. If the Neurology JRC agrees to include biomarker work in the ASO Development Candidate Identification Plan, the [***] is responsible for performing such biomarker work taking into consideration [***].

(c) **ASO Development Candidate Identification Term**. On a Collaboration Program-by-Collaboration Program basis, the term for the conduct of the applicable ASO Development Candidate Identification Plan (the "***ASO Development Candidate Identification Term***") will begin on the date the applicable Neurology Target becomes a Collaboration Target and will end upon the earlier of (i) designation of a Development Candidate for such Collaboration Program and (ii) the date on which Ionis notifies Biogen that, Ionis has in good faith determined that the identification of a Development Candidate under the applicable ASO Development Candidate Identification Plan is no longer technically feasible under the then-current state of the art (a "***Technical Failure***"). If Biogen disagrees with Ionis' determination that a Technical Failure has occurred, it may refer the matter to an independent qualified Third Party expert accepted by both Parties for final resolution of the dispute. The expert will use the information, materials and data provided to her or him by either Party to promptly resolve the dispute. The decision of the expert will be binding upon both Parties. [***] the costs of the expert. Should the Parties fail to agree on the expert within [***] days following either Party's request to nominate an expert under this Section 1.10.1(c), each Party will nominate an independent expert (who will not be a current or former employee of a Party or any of their Affiliates or have any personal or financial interest in a Party or any of their Affiliates), and promptly thereafter, those two independent experts will agree on the Third Party expert to resolve the dispute in accordance with this Section 1.10.1(c). In the event of any expert proceeding under this Section 1.10.1(c), Ionis will not be required to conduct the applicable ASO Development Candidate Identification Plan during the pendency of such proceeding. The Parties anticipate that the last ASO Development Candidate Identification Term will end approximately [***] years after the Effective Date.

(d) **End of ASO Development Candidate Identification Term**. At the end of the ASO Development Candidate Identification Term for a particular Collaboration Program that did not reach the Development Candidate stage, subject to Section 1.10.1(e), (i) neither Ionis nor Biogen will have an obligation to perform any activities under this Section 1.10 with respect to such Collaboration Program; (ii) such program will no longer be a Collaboration Program and the applicable gene target associated therewith will no longer be a Collaboration Target; (iii) Ionis' obligations and Biogen's rights under this Agreement with respect to the gene targets and any ASOs targeting such gene targets under such Collaboration Program will then terminate; and (iv) upon Ionis' request, Biogen will provide to Ionis any data generated under the Collaboration Program and licensed to Ionis under Section 4.3.2. For clarity, with respect to each Development Candidate that has reached the Development Candidate stage by the end of the ASO Development Candidate Identification Term, the expiration of the ASO Development Candidate Identification Term will not affect Ionis' obligation under Section 1.10.3 and Section 1.10.4 to Develop each such Development Candidate through the completion of the first PoC Trial.

(e) **Carryover Development Candidates**. If, by the end of the ASO Development Candidate Identification Term for a particular Collaboration Program, Ionis has not designated a Development Candidate for such Collaboration Program, and at any time during the [***] period after the end of the applicable ASO Development Candidate Identification Term Ionis' RMC designates an ASO discovered by Ionis that is designed to bind to the RNA that encodes the Collaboration Target for such Collaboration Program as a development candidate ready to start IND-Enabling Toxicology Studies (such ASO, a "***Carryover Development Candidate***"), then, Ionis will notify Biogen and will provide Biogen with the data package presented to Ionis' RMC to approve such Carryover Development Candidate. Biogen will then have [***] days from its receipt of such package to elect to enter into an amendment to this Agreement under the same terms as set forth in this Agreement (except that no additional upfront payment under Section 6.1 will be due). If, within [***] days after Biogen's receipt of such notice from Ionis, Biogen provides Ionis with written notice that it accepts such offer from Ionis for such Carryover Development Candidate, the Parties will execute an amendment to this Agreement regarding such Carryover Development Candidate on such terms. Otherwise, Ionis will have no further obligations and Biogen will have no further rights with respect to such Carryover Development Candidate.

1.10.2. Development Candidates; Initial Development Plans; Option Acceleration.

(a) **Appointment of JDC**. For each Development Candidate, the CSC will appoint a Neurology JDC approximately [***] days prior to the date Ionis expects to designate a Development Candidate. Such Neurology JDC can be either a new or existing Neurology JDC, but at least one of each Party's Neurology JDC members must have the relevant disease area expertise for the particular Development Candidate.

(b) **Development Candidate Data Package**. For each Collaboration Program, Ionis will notify the applicable Neurology JDC in writing within [***] days after designating a Development Candidate and will provide such Neurology JDC the applicable Development Candidate Data Package.

(c) **IND-Enabling Toxicology Studies**.

(i) For each Development Candidate under a Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, the applicable Neurology JDC will agree upon a high level pre-clinical toxicology strategy no later than [***] days following its receipt of the applicable Development Candidate Data Package. Ionis will conduct the IND-Enabling Toxicology Studies under such strategy to the extent consistent with the activities set forth on SCHEDULE 1.10.2(C); *provided, however*, if the initial strategy or applicable Initial Development Plan requires IND-Enabling Toxicology Studies that are in addition to or different from the activities set forth on SCHEDULE 1.10.2(C), then Biogen will pay Ionis the costs of such additional or different activities to the extent such costs exceed [***]% of the costs of the activities set forth on SCHEDULE 1.10.2(C). Such additional costs will be Biogen-Approved Costs and will be handled in accordance with the process described in Section 1.14.1.

(ii) For each ALS Collaboration Program and each Biogen Conducted Non-ALS Collaboration Program, the applicable Neurology JDC will agree upon a high level pre-clinical toxicology strategy no later than [***] days following its receipt of the applicable Development Candidate Data Package. In addition, the applicable Neurology JDC will approve any study protocols for the IND-Enabling Toxicology Studies at least [***] months prior to the anticipated commencement of such IND-Enabling Toxicology Studies. If the Neurology JDC is unable to agree on such high level pre-clinical toxicology strategy or study protocols for a particular ALS Collaboration Program or Biogen Conducted Non-ALS Collaboration Program within the applicable time period as set forth above in this Section 1.10.2(c)(ii), the matter will be referred to the CSC for resolution. If the CSC cannot agree on such a high level pre-clinical toxicology strategy within [***] days after the matter is so referred, or on any such study protocol within [***] days after the matter is so referred, as applicable, then Biogen will have final decision-making authority with respect thereto for IND-Enabling Toxicology Studies conducted by Biogen. Solely with respect to the first ALS Collaboration Program to have a Development Candidate, Ionis will conduct the IND-Enabling Toxicology Studies utilizing the same mechanics as set forth in Section 1.10.2(c)(i), and upon Initiation of such IND-Enabling Toxicology Studies Biogen will pay Ionis the applicable milestone payment under Section 6.5, which IND-Enabling Toxicology Studies are complete as of the Amendment Date for the Collaboration Program for [***]. Biogen will conduct, [***], all other IND-Enabling Toxicology Studies for the ALS Collaboration Programs and the Biogen Conducted Non-ALS Collaboration Programs, *provided* that Ionis may perform study analyses with respect to the Biogen Conducted Non-ALS Collaboration Programs if mutually agreed by the Parties. If, with respect to a particular ALS Collaboration Program or a particular Biogen Conducted Non-ALS Collaboration Program, Biogen desires Ionis to provide consulting or advisory services, and Ionis agrees to perform such services, Biogen will pay the costs of performing such services using the payment mechanisms set forth in Section 1.14.1.

For each ALS Collaboration Program and each Biogen Conducted Non-ALS Collaboration Program (other than the Collaboration Program for [***]), provided Ionis has delivered the API to support the IND-Enabling Toxicology Studies for such Collaboration Program to Biogen under Section 1.10.6 at least [***] days prior to the anticipated commencement of IND-Enabling Toxicology Studies for such Collaboration Program (subject to Biogen's timely delivery of an order for such API), Biogen will Initiate the first IND-Enabling Toxicology Study for such Collaboration Program within [***] days following Biogen's receipt of the applicable Development Candidate Data Package. If Biogen does not Initiate the first IND-Enabling Toxicology Study for such Collaboration Program within [***] days following Biogen's receipt of the applicable Development Candidate Data Package, if Ionis delivered the API to support the IND-Enabling Toxicology Studies for such Collaboration Program to Biogen under Section 1.10.6 at least [***] days prior to the anticipated commencement of IND-Enabling Toxicology Studies for such Collaboration Program, then Biogen will be deemed to have terminated this Agreement under Section 10.2.1 solely with respect to such Collaboration Program; *provided, however*, that if there is a delay in Initiating such IND-Enabling Toxicology Study caused by a condition outside of Biogen's control (including a delay by a Third Party vendor or a delay in supply of API from Ionis from the timeline described in this Section 1.10.2(c)(ii)), Biogen shall be excused from Initiating such IND-Enabling Toxicology Study for so long as such condition continues, and this Agreement shall not be deemed to be terminated with respect to such Collaboration Program, for so long as such condition continues.

With regard to the Collaboration Program for [***], notwithstanding any provision to the contrary in this Agreement, within [***] days following Biogen's receipt of the data generated from the 13 week monkey [***] biomarker study, Biogen will notify Ionis whether it has received all necessary internal approvals to commence Development of [***]. If Biogen does not notify Ionis within such [***]-day period that it has received all necessary internal approvals to commence Development of [***], Biogen will be deemed to have terminated this Agreement under Section 10.2.1 solely with respect to such Collaboration Program. If Biogen notifies Ionis within such [***]-day period that it has received all necessary internal approvals to commence Development of [***], Biogen shall, within [***] days of the later of the date of delivery of such notice and Biogen's receipt from Ionis of an invoice for such amount, pay Ionis an amount equal to $[***] for the API Ionis will supply to Biogen to support such Collaboration Program. If Biogen does not pay Ionis an amount equal to $[***] for such API within the time period described in the preceding sentence, then, if Ionis notifies Biogen in writing of such failure to pay and Biogen has not cured such payment failure within [***] days of such written notice, Biogen will be deemed to have terminated this Agreement under Section 10.2.1 solely with respect to such Collaboration Program.

(d) **Initial Development Plans**. For each Development Candidate under a Collaboration Program, within [***] days after designation of such Development Candidate, the applicable Neurology JDC will agree on an appropriate clinical development plan for such Development Candidate through completion of the first PoC Trial (each, an "***Initial Development Plan***"). With respect to each ALS Collaboration Program and each Biogen Conducted Non-ALS Collaboration Program, Biogen shall propose the initial draft of such Initial Development Plan to the Neurology JDC for review, comment and approval. With respect to each Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, Ionis shall propose the initial draft of such Initial Development Plan to the Neurology JDC for review, comment and approval. In each case, any such initial draft of an Initial Development Plan shall include the information set forth on SCHEDULE 1.10.2(d). If the Neurology JDC cannot agree upon the Initial Development Plan for a particular Collaboration Program, the matter will be referred to the CSC for resolution. If the CSC cannot agree on the Initial Development Plan within [***] days after the matter is so referred, [***] will have final decision-making authority with respect to the contents of the Initial Development Plan. In addition, prior to the Initiation of the first Clinical Study under the Initial Development Plan for a Collaboration Program, the Parties will endeavor to mutually agree on a communication plan regarding the public disclosure of data and results arising from such Collaboration Program; *provided*, *that* if the Parties cannot agree on such a communication plan, then [***] will have final decision-making authority regarding any such communications occurring prior to Option exercise.

(i) The Party responsible for conducting the Clinical Studies under a Collaboration Program will file and maintain the IND and other communications with Regulatory Authorities for each Collaboration Program consistent with Section 5.2.1. Notwithstanding the foregoing, with respect to each Collaboration Program for which Biogen is responsible for conducting the Clinical Studies, including each ALS Collaboration Program and each Biogen Conducted Non-ALS Collaboration Program, Ionis shall provide such reports and/or data as reasonably requested by Biogen generated from Ionis' activities performed under the applicable Initial Development Plan ("***Ionis Activities Data***") that may be useful in support of the IND for the Development Candidate under such Collaboration Program; *provided, that*, if, after receiving the Ionis Activities Data, Biogen requests that Ionis provide Biogen with additional information outside of the scope of the Ionis Activities Data that Biogen reasonably believes is necessary or useful to support the IND, then, to the extent such additional information is in Ionis' possession and delivering such data to Biogen will not breach any obligation Ionis owes to a Third Party, Ionis will promptly deliver such additional information to Biogen solely for Biogen to use to support the IND. [***] will bear the cost of the transfer of such additional information to Biogen pursuant to the preceding sentence; *provided*, that if [***] would incur out-of-pocket costs in excess of $[***] or FTE Costs in excess of the equivalent of [***] for one FTE at the then-applicable Ionis FTE Rate in connection with the delivery of such additional information, then [***] shall reimburse [***] for such excess.

(ii) If the requirements of the Phase 1 Trial Design for a Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program require (i) more than [***] human subjects, including single ascending dose and multiple ascending dose arms, or (ii) dosing longer than [***], then Ionis may elect to either (1) conduct such larger or longer Phase 1 Trial (in which case Section 1.10.2(e) will apply), or (2) have Biogen conduct such Phase 1 Trial. If Ionis elects to have Biogen conduct such Phase 1 Trial, then Biogen will conduct the Phase 1 Trial with Ionis' reasonable cooperation and in lieu of the applicable milestone payment payable to Ionis pursuant to Section 6.4 (as calculated in accordance with Section 1.10.2(e)) with respect to such Phase 1 Trial, Biogen will pay Ionis a milestone payment equal to $[***].

(iii) If the Initial Development Plan relates to an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, then Biogen will conduct the Phase 1 Trial and will pay Ionis a milestone payment in the amount as set forth in TABLE 2 of Section 6.5 or TABLE 1 of Section 6.4, as applicable.

(iv) Based on such Initial Development Plan, the CSC will update SCHEDULE 5.1.4 to add Specific Performance Milestone Events related to Biogen's Development and Commercialization of the Development Candidate following Option exercise, which Specific Performance Milestone Events will be generally consistent with Biogen's development timelines for its other drug development programs of similar stage and market potential. If the CSC cannot unanimously agree upon the Specific Performance Milestone Events for a particular Collaboration Program within [***] days after the date the CSC started discussing such Specific Performance Milestone Events, the matter will be referred to expert resolution pursuant to Section 12.1.4. Ionis will update each Initial Development Plan as needed, but at least once Annually, and submit it to the applicable Neurology JDC for its review and approval. If the applicable Neurology JDC cannot agree on the contents of any updated Initial Development Plan, the matter will be resolved in accordance with the procedures for establishing the Initial Development Plan set forth in this Section 1.10.2(d).

(v) The study synopsis for each Clinical Study for a Collaboration Program other than an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program shall be agreed on by the applicable Neurology JDC no later than [***] months prior to the anticipated Initiation of such Clinical Study, and shall contain the information set forth on SCHEDULE 1.10.2(d)(v) with respect to the applicable Clinical Study.

(e) **Cost Estimates**. After designation of a Development Candidate under a Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, the applicable Neurology JDC will agree on an initial estimate of the expected cost for Ionis to conduct the work [***] specified in the applicable Initial Development Plan, including Ionis' expected [***] and [***] costs (each, a "***Cost Estimate***"). The initial Cost Estimate [***] shall be agreed on by the applicable Neurology JDC no later than [***] months prior to the anticipated [***]. Based on the Cost Estimates, the Neurology JDC will establish the [***] and [***] milestone payments for such Collaboration Program, which payments will be equal to (i) [***]; plus (ii) [***]. The Parties will promptly negotiate in good faith using the Ionis/Biogen Additional Agreements as a basis for Cost Estimates and, if the total milestone payment [***] is more than $[***], the Parties will apportion such total milestone payment into smaller milestone payments in accordance with SCHEDULE 1.10.2(e); *provided, however*, that if [***], then the Neurology JDC shall determine whether and how to apportion such total milestone payment into smaller milestone payments. Each such smaller milestone payment shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen following the event that triggered such milestone payment. If the total milestone payment [***] is $[***] or less, then such milestone payment shall become due in its entirety upon [***], and shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen following [***]. As part of this process, Ionis will provide the Neurology JDC with a good faith estimate of the cost to conduct the work necessary to develop such Development Candidates under the applicable Initial Development Plan using a similar methodology as used under the Ionis/Biogen Additional Agreements. [***] months prior to the [***], using the process set forth above, the Neurology JDC will re-assess the total cost of such [***] and, if the cost has changed from the initial Cost Estimate, the Neurology JDC will adjust the applicable milestone payment accordingly, with any such adjustment to be agreed in writing to no later than the date that is [***] months prior to the [***]. Once there is less than [***] months prior to the [***], or such [***], if there are any changes to such [***] in accordance with this Agreement that result in an increase to the cost of such [***], then (a) if such cost is increased by more than [***], such increased costs will constitute an additional milestone payment to be paid in accordance with the provisions of this Section 1.10.2(e), or (b) if such cost is increased by [***], such increase will not affect the milestone payments for such [***] established under this Section 1.10.2(e), but instead will be handled in accordance with Section 1.14.1. For clarity, with respect to any increase in the cost of a [***] by more than [***]% under clause (a) of the preceding sentence, if such increased costs total $[***] or less and such [***], then such increased costs shall become due in their entirety immediately, and shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen. If the Neurology JDC cannot agree on the Cost Estimates within [***] days of receiving the proposed Cost Estimate, the matter will be referred to the CSC for resolution. Once the Neurology JDC has agreed on a Cost Estimate and/or the [***] milestone payments for such Collaboration Program are established under this Section 1.10.2(e) or Section 1.14.1, such agreement will be documented in a written side letter, in the form and format attached hereto as APPENDIX 4, which shall be executed by both Parties.

(f) **Obligation to Start Development Activities**. Ionis will not be required to conduct any Development activities for a Development Candidate if the Initial Development Plan, Specific Performance Milestone Events and the corresponding Cost Estimates have not been agreed to pursuant to this Section 1.10.2. Prior to such time as the Parties mutually agree on such Cost Estimate and/or the applicable [***] milestone payments and have executed a written side letter with respect to the foregoing in accordance with Section 1.10.2(e), Ionis may, in its discretion, commence Development activities for which it is responsible under this Agreement; *provided*, *however*, that Biogen will not be responsible for any costs of such Development activities if commenced by Ionis prior to the execution of any such side letter unless and until such a side letter has been executed by the Parties, and in no event will Biogen be responsible for any amounts incurred by Ionis for such Development activities in excess of amounts set forth in the side letter executed by the Parties with respect to such Development activities.

(g) **Option Acceleration**. If the PoC Trial for a Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program will be [***] or more, or require more than [***], then, if Ionis provides to Biogen the notice described in the following sentence, Ionis will not be required to conduct such PoC Trial for such Collaboration Program. Ionis will notify Biogen within [***] after finalization of the initial PoC Trial Design pursuant to Section 1.10.2(d) (or each time there is a material change thereto) for a Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program if Ionis elects not to conduct such PoC Trial for such Collaboration Program (such notice, an "***Option Acceleration Notice***"). If Ionis has delivered an Option Acceleration Notice as provided in this Section 1.10.2(g), Biogen will have [***] from its receipt of the data generated under the [***] for the first Phase 1 Trial for such Collaboration Program (an "***Option Acceleration Deadline***") to exercise its Option for the applicable Collaboration Program. If Biogen does not exercise its Option for the applicable Collaboration Program by the applicable Option Acceleration Deadline, Biogen's Option under Section 3.1 with respect to such Collaboration Program will expire and such Collaboration Program will terminate.

After Biogen's receipt of an Option Acceleration Notice with respect to a particular Collaboration Program, the Parties will mutually agree on the contents of all correspondence with and submissions to Regulatory Authorities to the extent related to the PoC Trial for the applicable Collaboration Program; *provided, however*, that if the Parties cannot so mutually agree, then [***] will have final decision-making authority but will not deliver any correspondence to Regulatory Authorities related to the PoC Trial for the applicable Collaboration Program that is not mutually agreed by the Parties unless [***] determines such correspondence is required to be delivered and cannot be delayed.

(h) **Attaching Plans to Neurology JDC Minutes**. The Neurology JDC will attach each Initial Development Plan and, if applicable, associated Cost Estimates to the minutes of the Neurology JDC for the meeting at which such Initial Development Plan and, if applicable, Cost Estimates were agreed. For clarity, such Initial Development Plan and Cost Estimates need not be agreed to at the same meeting of the Neurology JDC.

1.10.3. **Development Term**. The term for the conduct of the Drug Development Program will begin on the designation of the first Development Candidate and will end upon the earlier of (i) completion of the Initial Development Plans under all Collaboration Programs, which the Parties estimate will be approximately [***] years after the Effective Date, (ii) exercise by Biogen of its Option for all Collaboration Programs; (iii) the termination of the last Collaboration Program; and (iv) mutual agreement of the Parties to terminate the Drug Development Program.

1.10.4. **Drug Development**.

(a) ***Collaboration Programs Other than ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs*.** For each Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, Ionis will use Commercially Reasonable Efforts to conduct all activities under each Initial Development Plan on the timeline set forth in the applicable Initial Development Plan. For each Biogen Conducted Non-ALS Collaboration Program, Ionis will use Commercially Reasonable Efforts to conduct all activities allocated to Ionis under each Initial Development Plan on the timeline set forth in the applicable Initial Development Plan. Without limiting the foregoing, Ionis may discontinue Development under an Initial Development Plan if after having consulted, and having given good faith consideration to the recommendations of the Neurology JDC and a mutually-agreed Third Party expert, Ionis in good faith believes that continuing such Development would (i) pose an unacceptable risk or threat of harm in humans, or (ii) violate any Applicable Law, ethical principles, or principles of scientific integrity. Prior to discontinuing Development under an Initial Development Plan, Ionis will provide Biogen with reasonable advance notice of such discontinuation, including the grounds for Ionis' determination. If Ionis elects to discontinue Development under an Initial Development Plan pursuant to this Section 1.10.4(a), Biogen may, in its discretion, elect to continue Development of the applicable Development Candidate by providing Ionis with written notice of Biogen's exercise of the Option within [***] after Ionis' written notice to Biogen of such discontinuation and [***]. If Biogen does not timely exercise its Option under this Section 1.10.4(a), then the Option will expire.

(b) ***Phase 1 Trials***. Each Phase 1 Trial will be conducted in accordance with the applicable Phase 1 Trial Design set forth in the applicable Initial Development Plan.

(i) At meetings of the applicable Neurology JDC and at other times as appropriate, Ionis will keep Biogen informed of the progress and status of each Phase 1 Trial conducted by Ionis. When [***] under a Phase 1 Trial, Ionis will notify Biogen in writing of such [***] within [***] days of the conclusion of such Phase 1 Trial. Ionis will provide Biogen with the data generated under the [***] for such Phase 1 Trial as soon as practicable after such notice.

(ii) If Biogen conducts a Phase 1 Trial for a Collaboration Program, including an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, at meetings of the applicable Neurology JDC and at other times as appropriate, Biogen will keep Ionis informed of the progress and status of such Phase 1 Trial. When Biogen [***] a Phase 1 Trial, Biogen will notify Ionis in writing of such [***] within [***] days of the conclusion of such Phase 1 Trial. Biogen will provide Ionis with the data generated under the [***] for such Phase 1 Trial as soon as practicable after such notice.

(c) ***PoC Trial***. Each PoC Trial will be conducted in accordance with the PoC Trial Design set forth in the applicable Initial Development Plan.

(i) At meetings of the applicable Neurology JDC and at other times as appropriate, Ionis will keep Biogen informed of the progress and status of each PoC Trial conducted by Ionis. When Ionis [***] a PoC Trial under the applicable Initial Development Plan, Ionis will notify Biogen in writing within [***] days after such [***]. Ionis will provide Biogen with the [***] as soon as practicable after such notice.

(ii) If Biogen conducts a PoC Trial for a Collaboration Program, including an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, then at meetings of the applicable Neurology JDC and at other times as appropriate, Biogen will keep Ionis informed of the progress and status of the PoC Trial for such Collaboration Program. When Biogen completes such PoC Trial, Biogen will notify Ionis in writing within [***] days after such completion, and will provide Ionis with [***] as soon as practicable after such notice.

1.10.5. **Briefing the Neurology JRC, Neurology JDC and CSC; Conduct of Research and Development**. At each regularly scheduled meeting of the Neurology JRC, the Parties will provide progress updates on (i) the Neurological Disease Research Program and progress toward achieving Target Sanction for each High Interest Target and progress related to ALS Targets; (ii) activities conducted under the Core Research Program; (iii) progress under each ASO Development Candidate Identification Plan toward designating a Development Candidate; (iv) activities on the Deferred Targets conducted pursuant to Section 1.8.4, and (v) the progress of any Ionis Neurology Targets (including the estimated time for each Ionis Neurology Target to achieve Target Sanction), in each case, together with a summary of data associated with each Party's research and/or Development activities for each Collaboration Program. At each Neurology JDC meeting, the Parties will provide progress updates on activities conducted under the Initial Development Plans for the applicable Development Candidates, together with a summary of data associated with each Party's Development activities for the applicable Collaboration Program. At each CSC meeting, the Parties will provide any information reasonably requested by the members of the CSC in advance of such meeting.

1.10.6. **Clinical Supplies by Ionis**. For Collaboration Programs that are not ALS Collaboration Programs or Biogen Conducted Non-ALS Collaboration Programs, Ionis, at its expense, will supply API (on its own or through a CMO approved by Biogen) and Clinical Supplies to support the Research and Development activities under each Neurology Plan through Option exercise. If Biogen exercises an Option for a Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program at least [***] prior to the planned Initiation of the PoC Trial for the applicable Collaboration Program, Biogen may elect to either have (a) Ionis supply Clinical Supplies for such PoC Trial (on its own or through a CMO approved by Biogen), in which case Biogen will pay Ionis an amount equal to [***], or (b) a CMO supply Clinical Supplies for such PoC Trial in accordance with the Manufacturing Agreement entered into with such CMO. If Biogen exercises an Option for a Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program prior to, but less than [***] before, the planned Initiation of the PoC Trial for the applicable Collaboration Program, Ionis will supply Clinical Supplies for such PoC Trial (on its own or through a CMO approved by Biogen) and Biogen will pay Ionis an amount equal to [***]. For ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs, Ionis will supply API (on its own or through a CMO approved by Biogen) for clinical purposes in accordance with SCHEDULE 1.10.6, and such supply will be at Biogen's expense using the mechanism set forth in Section 1.14.1, and Biogen will be responsible for all other aspects of Clinical Supply for such clinical activities.

1.10.7. **Collaborations with Academics and Non-Profit Institutions**. Each Party (the "***Contracting Party***") may engage one or more academic or non-profit institutions to conduct work under any Neurology Plan or on any High Interest Target, Collaboration Target or Deferred Target, *provided however* that, with respect to any such academic or non-profit institution engaged to conduct such activities with respect to a High Interest Target, Collaboration Target or Deferred Target where such engagement begins after the date such High Interest Target, Collaboration Target or Deferred Target is designated, (i) the Contracting Party shall provide the other Party with an opportunity to comment on the proposed terms of any agreement or amendment to an existing agreement to be entered into with such institution, and (ii) so long as the other Party provides the Contracting Party such comments within [***] days of receiving a draft of such agreement from the Contracting Party, the Contracting Party will [***]. The Contracting Party will not be responsible for [***] as a result of the other Party's [***] to the terms of any agreement with any such academic or non-profit institution.

1.11. **Resource Allocations**. During the first [***] following the Effective Date, Ionis will use Commercially Reasonable Efforts to build a team of [***] FTEs to perform the activities under the Core Research Plan, the Neurological Disease Research Plan, and the target validation activities contemplated under SCHEDULE 1.2.4; and thereafter until the sixth anniversary of the Effective Date, Ionis will dedicate [***] FTEs to perform such activities; *provided*, Ionis may utilize such number of such [***] FTEs to perform drug discovery activities on ALS Targets as agreed by the Neurology JRC. At all times during such period, such FTEs will have experience and qualifications similar to that of the FTEs initially assigned to perform such activities hereunder. Biogen will be responsible for devoting its resources toward specific research efforts under the Core Research Program and Neurological Disease Research Program as reasonably determined by Biogen. During the [***] after the Effective Date, [***] of Ionis' [***] FTEs will be allocated to activities focused on core technology research and the Neurology JRC will determine the appropriate allocation of resources thereafter. Ionis will update the Neurology JRC at each meeting thereof on the utilization of such FTEs and provide the Neurology JRC with summaries of resource and FTE utilization in a format mutually agreed to by each Party's Alliance Managers. Biogen may also choose to supplement Ionis' efforts under the Core Research Plan and the Neurological Disease Research Plan with its own scientists at various points throughout the Research Term. After the sixth anniversary of the Effective Date, Ionis will provide sufficient resources to perform its obligations under each Collaboration Program as reasonably determined by Ionis.

1.12. **Research and Development Costs Paid by Ionis.**

1.12.1. **Research Programs**. During the Research Term, Ionis will be responsible for all Ionis Activities under the Core Research Program and the Neurological Disease Research Program, and all costs and expenses associated therewith.

1.12.2. **Collaboration Programs**. During the Option Period, on a Collaboration Program-by-Collaboration Program basis, Ionis will be responsible for all Ionis Activities under the ASO Development Candidate Identification Plan and the Initial Development Plan and, except as otherwise provided under Section 1.13.1, all costs and expenses associated therewith.

1.13. Research and Development Costs Paid by Biogen.

1.13.1. Before Option Exercise.

(a) **Research Programs**. During the Research Term, Biogen will be responsible for all Biogen Activities under the Core Research Program and Neurological Disease Research Program, and all costs and expenses associated therewith.

(b) **Collaboration Programs**. During the Option Period, on a Collaboration Program-by-Collaboration Program basis, Biogen will be responsible for any Biogen Activities under the ASO Development Candidate Identification Plan and the Initial Development Plan and all costs and expenses associated therewith. In addition, Biogen will be responsible for paying any Biogen-Approved Costs resulting from Biogen-Approved Changes using the payment mechanisms set forth in Section 1.14.

(c) **Additional Activities Approved by Biogen**. If, with respect to a particular Collaboration Program, Biogen desires that either Ionis or a Third Party [***] or conduct other work to support Approval of a Collaboration Product, including [***], prior to Option exercise, and Ionis agrees to perform such work, Biogen will pay the costs of conducting such work using the payment mechanisms set forth in Section 1.14.1.

1.13.2. **After Option Exercise**. After Option exercise, Biogen will be solely responsible for the costs and expenses related to the Development, Manufacture and Commercialization of Collaboration Products, including any work performed by Ionis at Biogen's request, and all supply chain planning and decision-making.

1.14. Payment Mechanisms.

1.14.1. **Payment Mechanics for Additional Activities Approved by Biogen**. Biogen will pay Ionis (1) costs resulting from requests from Biogen that Ionis perform additional work under this Agreement, including, the cost of Ionis' time incurred in performing such work at the then-applicable Ionis FTE Rate ("***FTE Costs***"), the cost of [***], and any [***] incurred by Ionis in performing such work, or (2) Additional Plan Costs resulting from Biogen-Approved Changes (such costs, collectively "***Biogen-Approved Costs***"). For clarity, the Biogen-Approved Costs shall include Additional Plan Costs for a [***] that result from changes to such [***] made after the milestone payment with respect to such [***] is agreed upon in writing by the Parties pursuant to Section 1.10.2(e), if such cost is increased by [***] as described in Section 1.10.2(e)). For the avoidance of doubt, if such cost is increased by more than [***] as described in Section 1.10.2(e)), such increased costs will constitute an additional milestone payment to be paid in accordance with the provisions of Section 1.10.2(e), and will not be handled under this Section 1.14.1. Ionis will permit Biogen to review, negotiate (with Ionis) and approve (including through the Neurology JDC) all Biogen-Approved Costs; *provided* Biogen will provide a substantive, good faith response within [***] days of Ionis' request for approval. For clarity (i) this Section 1.14.1 will not be used to establish the initial milestone payments under Section 1.10.2(e), and (ii) expenses paid under Section 1.14.1(a) and Section 1.14.1(b) are not subject to reconciliation. Once Biogen-Approved Costs are mutually agreed under this Section 1.14.1, such agreement will be documented in a written side letter, in the form and format attached hereto as APPENDIX 4, which shall be executed by both Parties. Prior to such time as the Parties mutually agree on such Biogen-Approved Costs and have executed a written side letter with respect to the foregoing, Ionis may, in its discretion, commence Development activities for which it is responsible under this Agreement; *provided, however*, that Biogen will not be responsible for any costs of such Development activities if commenced by Ionis prior to the execution of any such side letter unless and until such a side letter has been executed by the Parties, and in no event will Biogen be responsible for any amounts incurred by Ionis for such Development activities in excess of amounts set forth in the side letter executed by the Parties with respect to such Development activities.

(a) For Biogen-Approved Costs resulting from [***], or from [***] that are made after the milestone payment with respect to such [***] is agreed upon in writing by the Parties pursuant to Section 1.10.2(e), Biogen will pay Ionis for such Biogen-Approved Costs [***] within [***] days after receipt of the applicable invoice by Biogen following [***], or the date that Biogen agrees to such changes to such [***], as applicable; *provided, however*, that if such Biogen-Approved Costs total more than $[***], the Parties will apportion such total Biogen-Approved Costs into smaller milestone payments in accordance with SCHEDULE 1.10.2(e) (or, if such Biogen-Approved Costs result from changes to a [***], then the Neurology JDC shall determine whether and how to apportion such Biogen-Approved Costs into smaller milestone payments). Each such smaller milestone payment shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen following the event that triggered such milestone payment. If such Biogen-Approved Costs total $[***] or less, then such Biogen-Approved Costs shall become due in their entirety upon [***] or the date that the Parties agree to such Biogen-Approved Costs, if such [***], and shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen following [***] or the date of such agreement regarding the Biogen-Approved Costs, as applicable.

(b) For Biogen-Approved Costs resulting from [***], Biogen will pay Ionis, in accordance with any applicable [***] entered into by the Parties after the Effective Date, for [***]% of such Biogen-Approved Costs within [***] days after receipt of the applicable invoice by Biogen following Biogen's request or approval for such [***], and the remaining [***]% within [***] days after receipt of the applicable invoice by Biogen following [***].

(c) For any Biogen-Approved Cost that (x) has an Estimated Biogen-Approved Cost of less than $[***] and (y) does not result from [***], from [***] that are made after the milestone payment with respect to such [***] is agreed upon in writing by the Parties pursuant to Section 1.10.2(e) or from [***], Ionis will invoice Biogen directly for such Biogen-Approved Cost in advance, on a [***] basis based upon the applicable Estimated Biogen-Approved Costs and Biogen will pay the invoices submitted pursuant to this Section 1.14.1(c) for such Biogen-Approved Costs within [***] days after receipt of the applicable invoice by Biogen. For purposes of this Section 1.14.1(c), "***Measurement Period***" means each [***].

(d) For any Biogen-Approved Costs that (x) has an Estimated Biogen-Approved Cost of $[***] or more and (y) does not result from [***], from [***] that are made after the milestone payment with respect to such [***] is agreed upon in writing by the Parties pursuant to Section 1.10.2(e) or [***], Ionis will invoice Biogen directly for such Biogen-Approved Cost in advance on a [***] basis based upon the applicable Estimated Biogen-Approved Costs and Biogen will pay the invoices submitted pursuant to this Section 1.14.1(d) for such Biogen-Approved Costs within [***] days after receipt of the applicable invoice by Biogen. For purposes of this Section 1.14.1(d), "***Measurement Period***" means each [***].

(e) Within [***] days after the end of the applicable Measurement Period, Ionis will provide Biogen with a written statement (1) reconciling the [***] the Estimated Biogen-Approved Costs and the [***] within the Biogen-Approved Costs (the "***Actual Biogen-Approved Costs***") incurred by Ionis during the just-ended Measurement Period and (2) confirming that the FTE Costs portion of the Estimated Biogen-Approved Costs is a reasonable approximation of the actual FTE Costs incurred by Ionis during the just-ended Measurement Period. If the Estimated Biogen-Approved Costs exceed the Actual Biogen-Approved Costs for such period, Ionis will, offset all such excess payments against any future invoices under this Agreement until Biogen has recouped all such overpayments. If the Estimated Biogen-Approved Costs are less than the Actual Biogen-Approved Costs for such period, Ionis will invoice Biogen for the remaining amounts owed to Ionis, and Biogen will pay such invoices within [***] days of receipt of such invoice. In the case where additional activities under this Section 1.14.1 are performed by a Third Party, the Parties will arrange for the Third Party to directly bill Biogen and for Biogen to pay such Third Party directly.

1.15. **Participation in Regulatory Meetings**. For each Collaboration Program, each Party will conduct its interactions and communications with Regulatory Authorities in accordance with Section 5.2.

1.16. **Participation in Meetings Sponsored by a Party's Clinical Development Group**. With respect to each Collaboration Program (including each ALS Collaboration Program and each Biogen Conducted Non-ALS Collaboration Program), each Party will provide the other Party with an invitation to attend, and allow such other Party to participate in, any meetings sponsored by a Party's clinical development group relating to the Development Candidate or the conduct or design of any Clinical Study; *provided*, *however*, that such first Party may exclude the other Party from any portions of such meetings that do not pertain to such Development Candidate or all of any such meeting if such Party determines that it is not feasible for the other Party to attend any such meeting because other products or matters will be discussed in combination with the Development Candidate at such meeting; and *provided*, *further*, that, the organizing Party will endeavor to structure such meetings that discuss topics unrelated to the Development Candidate in a manner that permits the non-organizing Party to attend (e.g., structuring the agenda of such meeting so that the Development Candidate is discussed first so that the non-organizing Party may attend that portion of such meeting only). With respect to any such meetings organized by a Party, the non-organizing Party shall comply with the organizing Party's internal policies disclosed to the non-organizing Party regarding attendance and participation in such meetings, and the non-organizing Party will participate in such meeting in a manner that is consistent with the organizing Party's strategy for the applicable Development Candidate. If a Party is excluded from any such meeting, the organizing Party will provide such Party with a written summary of the portions of such meeting relevant to such Development Candidate within [***] days after such meeting. For the avoidance of doubt, this Section 1.16 shall not apply to unplanned meetings or unplanned discussions with investigators or key opinion leaders. Biogen's obligation under this Section 1.16 to invite Ionis to attend and participate in any meetings organized by a Biogen will cease, on a Collaboration Product-by-Collaboration Product basis, on the date Biogen submits an NDA or MAA to a Regulatory Authority for such Collaboration Product.

1.17. **Impact of [***] Development Path**. If the Parties mutually agree to amend an Initial Development Plan for a Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, where such amended plan contemplates [***], then the Parties will make appropriate changes to the operational terms of this Agreement (e.g., [***]) to reflect such an [***] development plan, consistent with the comparable provisions necessary to support the development plan under the [***]; *provided*, that if the Initial Development Plan for a Biogen Conducted Non-ALS Collaboration Program contemplates such an [***] development path, then the Parties will determine by mutual agreement prior to commencing any [***] under such Initial Development Plan whether to designate such [***] for such Biogen Conducted Non-ALS Collaboration Program. Nothing in this Section 1.17 will affect either Party's rights or obligations under Section 1.10.2(g).

1.18. Research and Development Management.

1.18.1. Collaboration Steering Committee. The Parties will establish a Collaboration steering committee ("***CSC***") with the powers, roles and responsibilities set forth on SCHEDULE 1.18.1 and in this Section 1.18.1 to oversee the Collaboration. The CSC will consist of up to three representatives appointed by Ionis and up to three representatives appointed by Biogen. The Neurology JRC and Neurology JDC under this Agreement will report to the CSC. The CSC will determine the CSC operating procedures at its first meeting, including the CSC's policies for replacement of CSC members, policies for participation by additional representatives or consultants invited to attend CSC meetings, and the location of meetings, which will be codified in the written minutes of the first CSC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending CSC meetings. Any decision that may be made by the Neurology JRC or Neurology JDC may be made by the CSC and such decision by the CSC will have the same effect as if made by the Neurology JRC or the Neurology JDC under this Agreement. The CSC may delegate any of its functions specified in Section 1.18.1(a) below to a Neurology JDC by agreeing to and codifying such delegation in the minutes of the CSC.

(a) Role of the CSC. Without limiting any of the foregoing, subject to Section 1.18.4, the CSC will perform the following functions, some or all of which may be addressed directly at any given CSC meeting:

(i) approving the terms on which Biogen would develop and commercialize a Multi-Indication Product as described in APPENDIX 3;

(ii) determining the primary disease association of a Multi-Indication Target;

(iii) appointing a Neurology JDC for each Development Candidate under this Agreement, whether by creating a new Neurology JDC or assigning an existing Neurology JDC to oversee such Development Candidate;

(iv) establishing the Initial Development Plan in the event of a Neurology JDC dispute as described in Section 1.10.2(d);

(v) establishing the Specific Performance Milestone Events as described in Section 1.10.2(d)(iv);

(vi) establishing the [***] and [***] milestone payments if the Neurology JDC is unable to agree on such payments as described in Section 1.10.2(e);

(vii) reviewing and assessing reports provided by the Neurology JRC and the Neurology JDCs;

(viii) providing input to the JPC as appropriate;

(ix) reviewing and providing input on the CTDs and IDPs as appropriate;

(x) assisting with and participating in the resolution of disputes as contemplated in Section 12.1.1; and

(xi) such other review and advisory responsibilities as may be assigned to the CSC by the Parties pursuant to this Agreement.

1.18.2. **Neurology JRC**. The Parties will establish a joint research committee (the "***Neurology JRC***") reporting to the CSC, to provide advice and make recommendations on the conduct of activities under the Core Research Program, Neurological Disease Research Program and each Collaboration Program up to Development Candidate designation. The Neurology JRC will consist of up to three representatives appointed by Ionis and up to three representatives appointed by Biogen. Each Neurology JRC member will have experience and expertise appropriate for the Core Research Program, Neurological Disease Research Program and/or the stage of development of the Collaboration Programs. Each Party will designate one of its 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 Neurology JRC. The co-chairs will be responsible for overseeing the activities of the Neurology JRC consistent with the responsibilities set forth below in this Section 1.18.2. SCHEDULE 1.18.2 sets forth certain Neurology JRC governance matters agreed to as of the Effective Date. The Neurology JRC will determine the Neurology JRC operating procedures at its first meeting, including the Neurology JRC's policies for replacement of Neurology JRC members, policies for participation by additional representatives or consultants invited to attend Neurology JRC meetings, and the location of meetings, which will be codified in the written minutes of the first Neurology JRC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending Neurology JRC meetings. Ionis and Biogen will use reasonable efforts to schedule meetings of the Neurology JRC to take place at the same location and on the same dates as meetings of the CSC and the joint development and steering committees under the Ionis/Biogen Additional Agreements, to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses.

(a) **Role of the Neurology JRC**. Without limiting any of the foregoing, subject to Section 1.18.4, the Neurology JRC will perform the following functions, some or all of which may be addressed directly at any given Neurology JRC meeting:

(i) maintain the list of High Interest Targets, ALS Targets, Collaboration Targets, and Biogen Alternate Modality Targets, as such lists may be updated from time to time in accordance with this Agreement, and attach such lists to the minutes of the meeting of the Neurology JRC where any update to the High Interest Target List, ALS Target List or Collaboration Targets, Biogen Alternate Modality Targets occurred;

(ii) as described in Section 1.2.3(c), determine the number of High Interest Targets for which activities to support Target Sanction will be conducted during each year of the Research Term;

(iii) review and approve amendments to the Core Research Plan and the Neurological Disease Research Plan as described in Sections 1.2.2 and 1.2.3;

(iv) allocate resources under Section 1.11;

(v) determine the number of FTEs Ionis will use to perform drug discovery activities on ALS Targets;

(vi) as contemplated under Section 1.6.1, determine whether to re-allocate resources on additional Collaboration Programs;

(vii) during years [***] through [***] after the Effective Date, determine the appropriate allocation of Ionis' resources to the Core Research Plan, the Neurological Disease Research Plan and each ASO Development Candidate Identification Plan, as described in Section 1.11;

(viii) review the overall progress of Ionis' efforts to achieve Target Sanction with respect to each High Interest Target that has not achieved Target Sanction status;

(ix) as described in Section 1.3, review each Target Sanction Data Package and determine the best therapeutic modality to pursue for a High Interest Target;

(x) as described in Section 1.4, review each Target Sanction Data Package for an Ionis Neurology Target;

(xi) establish an ASO Development Candidate Identification Plan for each Collaboration Program as described in Section 1.10.1(a);

(xii) agree on any biomarker work to be performed in the ASO Development Candidate Identification Plan, and [***] is responsible for performing such biomarker work [***];

(xiii) as described in Section 1.10.2(c) and Section 1.10.2(d), agree upon a high level pre-clinical toxicology strategy and Initial Development Plan for each Development Candidate;

(xiv) review the overall progress of Ionis' efforts to discover, identify, optimize and select the Development Candidate for each Collaboration Program;

(xv) monitoring progress of each Collaboration Program and maintaining a calendar of anticipated milestone achievement dates for each Collaboration Program;

(xvi) establishing teams and committees to oversee and manage activities under the Core Research Program, Neurological Disease Research Program and each Collaboration Program up to Development Candidate designation as it deems necessary;

(xvii) discuss upcoming academic and non-profit collaborations that a Party is negotiating or considering entering into; and

(xviii) such other review and advisory responsibilities as may be assigned to the Neurology JRC by the CSC pursuant to this Agreement.

1.18.3. **Joint Development Committees**. For each Development Candidate, the CSC will appoint a joint development committee (each, a "***Neurology JDC***") approximately [***] days prior to the date Ionis expects to designate a Development Candidate, to govern the activities under this Agreement with respect to such Collaboration Program. Each Neurology JDC will report to the CSC and will consist of an equal number of representatives appointed by Ionis and Biogen. Each Neurology JDC member will be a senior clinical development leader or have other experience and expertise appropriate for the stage of development of the Collaboration Program in the applicable disease area, and at least one of each Party's members will have operational responsibility for the applicable Collaboration Program. Each Party will designate one of its 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 Neurology JDC. The co-chairs will be responsible for overseeing the activities of the Neurology JDC consistent with the responsibilities set forth below in this Section 1.18.3. SCHEDULE 1.18.3 sets forth certain Neurology JDC governance matters agreed to as of the Effective Date. Each Neurology JDC will determine its operating procedures at its first meeting, including the Neurology JDC's policies for replacement of Neurology JDC members, policies for participation by additional representatives or consultants invited to attend Neurology JDC meetings, and the location of meetings, which will be codified in the written minutes of the first Neurology JDC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending Neurology JDC meetings. If practical, Ionis and Biogen will use reasonable efforts to schedule meetings of each Neurology JDC to take place at the same location and on the same dates as meetings of the CSC and the joint development and steering committees under the Ionis/Biogen Additional Agreements, to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses.

(a) **Role of the Neurology JDCs**. Without limiting any of the foregoing, subject to Section 1.18.4, each Neurology JDC will perform the following functions, some or all of which may be addressed directly at any given Neurology JDC meeting:

(i) establish the Initial Development Plan for each Development Candidate and update such plan as needed as provided in Section 1.10.2(d);

(ii) agree on Cost Estimates and the [***] milestone payments under Section 1.10.2(e);

(iii) approve Biogen-Approved Costs pursuant to Section 1.14.1;

(iv) if the milestone payment agreed upon in writing by the Parties pursuant to Section 1.10.2(e) with respect to a [***] exceeds $[***], establishing whether and how such payment shall be apportioned into smaller milestone payments as described in Section 1.10.2(e);

(v) if any Biogen-Approved Costs that result from [***] exceed $[***], establishing whether and how such payments shall be apportioned into smaller milestone payments as described in Section 1.14.1(a);

(vi) establish a high-level preclinical toxicology strategy for each Collaboration Program under Section 1.10.2(c);

(vii) establishing teams and committees to oversee and manage activities under each Collaboration Program after Development Candidate designation as it deems necessary; and

(viii) such other review and advisory responsibilities as may be assigned to the Neurology JDC by the CSC pursuant to this Agreement.

1.18.4. **Decision Making**.

(a) **Committee Decision Making.** Decisions by each of the CSC, Neurology JRC and Neurology JDC will be made by unanimous consent with each Party's representatives having, collectively, one vote. At any given meeting of any such committee, quorum will have deemed to be reached if a voting representative of each Party is present or participating in such meeting. No action taken at any meeting of any such committee will be effective unless there is a quorum at such meeting. Unless otherwise specified in this Agreement, no action will be taken with respect to a matter for which the CSC, Neurology JRC or Neurology JDC, as applicable, has not reached unanimous consensus.

(b) **Implementation.** Each Party will give due consideration to, and consider in good faith, the recommendations and advice of the CSC, the Neurology JRC and Neurology JDC (as applicable) regarding the conduct of the Core Research Program, Neurological Disease Research Program and each Collaboration Program. Subject to Section 1.10.1 and Section 1.10.2, prior to Option exercise, (i) Ionis will have the final decision-making authority regarding [***] and (ii) Biogen will have the final decision-making authority regarding [***]. After Option exercise for a particular Collaboration Program, Biogen will have sole decision-making authority regarding [***] of Collaboration Products for such Collaboration Program, *provided, however,* that [***]. Except as otherwise expressly stated in this Agreement, the CSC, the Neurology JRC and Neurology JDC 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.

1.18.5. **Ionis Obligation to Participate in the Neurology JRC, Neurology JDC and CSC**. Ionis' obligation to participate in (i) the Neurology JRC, will terminate at the end of the ASO Development Candidate Identification Term, (ii) the Neurology JDC, will terminate upon Biogen's exercise (or expiration) of the Option for the last Collaboration Program, and (iii) the CSC, will terminate upon Biogen's exercise (or expiration) of the Option for the last Collaboration Program. Thereafter, for each such governing body, Ionis will have the right, but not the obligation, to participate in such meetings upon Ionis' request.

1.18.6. **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 CSC, the Neurology JRC and Neurology JDC, and performing the activities listed in SCHEDULE 1.18.6.

ARTICLE 2.
EXCLUSIVITY COVENANTS

2.1. **Exclusivity; Right of First Negotiation**.

2.1.1. **Exclusivity Covenants**.

(a) **The Parties' Exclusivity Covenants During the Research Term for High Interest Targets**. Each Party agrees that, *except* in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 1.8.4, Section 2.1.2, Section 2.2, Section 10.4.3 or Section 10.4.4, or as contemplated by any Neurology Plan, neither it nor any of its Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to the discovery, research, development, manufacture or commercialization in the Field of an oligonucleotide that is designed to bind to the RNA that encodes a High Interest Target from the Effective Date until the earlier to occur of (i) the date such target is removed from the High Interest Target List, by Biogen or ceases to be a High Interest Target by operation of this Agreement, or (ii) the date on which the High Interest Target List is dissolved in accordance with Section 1.9.

(b) **Ionis' Exclusivity Covenants During the Research Term for Ionis Neurology Targets**. Ionis agrees that neither it nor any of its Affiliates will work for the benefit of any Third Party (including the grant of any license to any Third Party that would diminish Biogen's rights under Section 1.4 or prevent Ionis from granting Biogen a license under Section 4.1.1) with respect to the discovery, research, development, manufacture or commercialization in the Field of an oligonucleotide that is designed to bind to the RNA that encodes an Ionis Neurology Target from the Effective Date until the earlier to occur of (i) the date such target ceases to be a Neurology Target by operation of this Agreement, or (ii) the expiration of the Research Term.

(c) **Ionis' Exclusivity Covenants for Biogen Alternate Modality Targets**. With respect to each Biogen Alternate Modality Target, *except* in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 2.1.2, Section 10.4.3 or Section 10.4.4, neither Ionis nor any of its Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to the discovery, research, development, manufacture or commercialization of an oligonucleotide designed to bind to the RNA encoding such Biogen Alternate Modality Target without Biogen's prior written consent; *provided, however*, that if (A) Biogen, its Affiliates or Sublicensees have not [***] within [***] (or, if Biogen has used Commercially Reasonable Efforts to [***], within [***]) after the date the applicable Neurology Target becomes a Biogen Alternate Modality Target in accordance with this Agreement, or (B) after [***], Biogen, its Affiliates and Sublicensees thereafter cease to use Commercially Reasonable Efforts to develop or commercialize such Product (or otherwise stops developing or commercializing such Product), then (i) the exclusive license granted to Biogen under Section 4.1.1(b) for such Biogen Alternate Modality Target will convert to a non-exclusive license, and (ii) Ionis and its Affiliates may independently or for or with any Third Party (including the grant of any license to any Third Party) research, develop, and commercialize oligonucleotides designed to bind to the RNA encoding such Biogen Alternate Modality Target (each such oligonucleotide, an "***Ionis Non-Exclusive Product***"), but not, for the avoidance of doubt, any molecule or product designed to [***] that is not [***], and the license to Biogen under Section 4.1.1(b) will become a non-exclusive license to the extent necessary to allow Ionis to conduct such activities.

(d) **The Parties' Exclusivity Covenants During the Option Period for Collaboration Targets**. Each Party agrees that, *except* in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 2.1.2, Section 2.2, Section 10.4.3 or Section 10.4.4, neither it nor any of its Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to discovery, research, development, manufacture or commercialization in the Field of an oligonucleotide that is designed to bind to the RNA that encodes a Collaboration Target from the date such gene target was designated a Collaboration Target under this Agreement through the expiration or earlier termination of the applicable Option Period.

(e) **The Parties' Exclusivity Covenants After Option Exercise**. *Except* in the performance of its obligations or exercise of its rights under this Agreement and except as set forth in Section 2.1.2, Section 2.2, Section 10.4.3 or Section 10.4.4, if Biogen timely exercises an Option in accordance with this Agreement, then neither Ionis nor Biogen nor their respective Affiliates will work independently or for or with any Third Party (including the grant of any license to any Third Party) with respect to:

(i) discovery, research or development in the Field of an oligonucleotide that is designed to bind to the RNA that encodes the applicable Collaboration Target related to such Option until [***]; and

(ii) on a country-by-country basis, commercializing in the Field an oligonucleotide that is designed to bind to the RNA that encodes such Collaboration Target until [***].

(f) **Failure to Defer or Designate a High Interest Target a Collaboration Target or Biogen Alternate Modality Target**. If, after a High Interest Target achieves Target Sanction, Biogen (i) fails to timely designate such High Interest Target as a Collaboration Target or a Biogen Alternate Modality Target (or, if applicable elect to defer under Section 1.3) on the applicable timelines set forth in Section 1.3 or Section 1.8, (ii) fails to timely pay the applicable milestone payment under Section 6.2.1 or Section 6.2.2, (iii) under Section 10.2.1 or Section 10.2.2 voluntarily terminates its license under Section 4.1.1(b) with respect to a High Interest Target Biogen designated as a Biogen Alternate Modality Target, or (iv) notifies Ionis that it has terminated an ALS Collaboration Program after the Initiation of a Phase 1 Trial for such program or fails to timely pay a milestone payment under Section 6.5 with respect to a particular ALS Collaboration Program, then in each case for a period of [***] after the date of such failure or such termination, as applicable, (x) neither Biogen nor its Affiliates will independently or for or with any Third Party (including the grant of any license to any Third Party) discover, research, develop, manufacture or commercialize an oligonucleotide designed to bind to the RNA encoding such High Interest Target and (y) if Biogen or any of its Affiliates or licensees discovers, researches, develops, manufactures or commercializes a Biogen Alternate Modality Product for such High Interest Target and such High Interest Target is not a Pre-Existing Target, then (A) the provisions of ARTICLE 6 will apply with respect to such Biogen Alternate Modality Product, (B) Biogen will pay Ionis all amounts owed (or which would have been owed absent such original failure or such termination) under such ARTICLE 6 with respect to such Biogen Alternate Modality Product (to the extent such amounts have not previously been paid with respect to the applicable Biogen Alternate Modality Target) in accordance with the terms hereof, (C) to the extent Ionis has the ability to do so, Ionis will grant Biogen the license under Section 4.1.1(b) with respect to such Biogen Alternate Modality Target, and (D) Section 2.1.1(c) will not apply with respect to such Biogen Alternate Modality Product. For the avoidance of doubt, nothing in this Agreement shall restrict Biogen's or its Affiliate's or licensee's discovery, research, development, manufacture, or commercialization of a product for a Pre-Existing Target that is not an oligonucleotide designed to bind to the RNA that encodes such Pre-Existing Target.

2.1.2. **Limitations and Exceptions to Ionis' Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Ionis' practice of the following will not violate Section 2.1.1, Section 2.2 or Section (d) of APPENDIX 3:

(a) Any activities pursuant to the Prior Agreements as in effect on the Effective Date;

(b) The granting of, or performance of obligations under, Permitted Licenses;

(c) The research, development or commercialization of an Ionis Multi-Indication Compound to the extent permitted under APPENDIX 3;

(d) The exercise of its rights under Section 3.2.2; and

(e) The development or commercialization of a Pre-Existing Competitive Product in accordance with Section 12.5.2 and Section 12.5.3.

2.1.3. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the RNA that encodes a Collaboration Target with the intent of treating a Neurological Disease in the Field. Ionis and Biogen are subject to exclusivity obligations under Section 2.1; *however*, the Parties acknowledge and agree that, except as otherwise provided herein, each Party and its Affiliates (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 a gene that is ***not*** (i) a High Interest Target to the extent Section 2.1.1(a) still applies, (ii) a Biogen Alternate Modality Target to the extent Section 2.1.1(c) still applies, or (iii) a Collaboration Target, in each case for any indication, even if such products are designed to treat a Neurological Disease.

2.2. **Right of First Negotiation for Follow-On Compounds**. On a Collaboration Program-by-Collaboration Program basis, during the period commencing on the Effective Date and ending upon (i) if the applicable Option is not exercised in accordance with this Agreement, [***], or (ii) if the applicable Option is exercised in accordance with this Agreement, [***] (such period, the "***ROFN Period***"), Ionis hereby grants to Biogen a right of first negotiation to develop and commercialize any Follow-On Compound developed by or on behalf of Ionis, which right of first negotiation is granted on the following terms and conditions:

2.2.1. Within [***], Biogen may provide Ionis with a non-binding, good faith written notice expressing Biogen's desire for Ionis to identify a Follow-On Compound (a "***Follow-On Interest Notice***"). If (i) Biogen does not, within such [***] period, provide Ionis with a Follow-On Interest Notice, or (ii) Biogen does timely provide Ionis 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 date of Option exercise, then, Ionis 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 the ROFN Period, Ionis will not grant any license (or an option to obtain such a license) under any intellectual property owned, controlled or licensed by Ionis to make, use or sell any Follow-On Compound (a "***Follow-On Agreement***") *unless and until* Ionis provides a written notice to Biogen (a "***Follow-On Negotiation Notice***"), which notice identifies [***]. Ionis will not initiate negotiations regarding or enter into such a Follow-On Agreement with any Third Party until [***].

2.2.2. If Biogen or one of its Affiliates responds within [***] after its receipt of the Follow-On Negotiation Notice indicating that Biogen or one of its Affiliates desires to negotiate with Ionis regarding the proposed Follow-On Agreement, Ionis and Biogen or one of its Affiliates will negotiate in good faith with each other until the [***] after the date Ionis provided Biogen the Follow-On Negotiation Notice (or such other period as mutually agreed by the Parties) (the "***Negotiation Period***") regarding a mutually satisfactory Follow-On Agreement (which may take the form of an amendment to this Agreement). During the Negotiation Period, Ionis will make at least [***] to Biogen or its Affiliate setting forth all material business and legal terms on which Ionis would be willing to enter into the proposed Follow-On Agreement with Ionis; *provided, that* neither Party will have any obligation to enter into a Follow-On Agreement. If the Negotiation Period expires before Biogen or its Affiliate and Ionis have entered into such a Follow-On Agreement, Ionis will have no further obligation to negotiate with Biogen or its Affiliates with respect to such Follow-On Agreement and Ionis will be free to negotiate and enter an agreement with a Third Party with respect to a Follow-On Agreement [***]; *provided, however*, that Ionis will not enter into any such Follow-On Agreement with any Third Party unless the terms and pricing of such Follow-On Agreement, [***] during the Negotiation Period. If, with respect to any Follow-On Compound that was the subject of the Follow-On Agreement previously discussed by the Parties, after the end of the Negotiation Period and prior to Ionis entering into a Follow-On Agreement with a Third Party, [***] regarding the Follow-On Compound, Ionis' obligations and Biogen's rights under Section 2.2.1 and this Section 2.2.2 will reset and Ionis will provide Biogen with a new Follow-On Negotiation Notice.

2.2.3. Any Follow-On Agreement entered into by Ionis with a Third Party in accordance with Section 2.2.2 will be a Permitted License to the extent related to the Follow-On Compound.

2.2.4. Notwithstanding anything to the contrary in this Agreement, until [***], Ionis will provide to Biogen a Follow-On Negotiation Notice for each [***] pursuant to this Section 2.2, *unless* Ionis enters into a Follow-On Agreement with a Third Party pursuant to this Section 2.2 and the terms of such agreement do not permit Ionis to grant Biogen rights with respect to the applicable Follow-On Compound.

Except as expressly set forth in Section 2.1.2, Section 2.2, or Section 10.4.4, in no event will Ionis have the right to [***].

ARTICLE 3.
EXCLUSIVE OPTION

3.1. Option.

3.1.1. **Advance Data Disclosure**. On or about 90 days before the date on which Ionis estimates that the database will be locked for the first PoC Trial for a particular Collaboration Program that is being conducted by Ionis (each an "***Estimated Lock Date***"), Ionis will provide Biogen with a written notice of such Estimated Lock Date. If Biogen provides written notice to Ionis [***] after Biogen's receipt of the notice regarding the Estimated Lock Date that Biogen has a good faith intention to exercise the Option for the applicable Collaboration Program under Section 3.1.3, then as soon as reasonably practicable after Ionis receives such notice from Biogen, Ionis will provide Biogen with an early preview of the information to be included in the [***] for the applicable Collaboration Program to the extent then in Ionis' possession and not already provided to Biogen, to assist Biogen with its decision of whether to exercise the Option. Within 15 Business Days after Biogen's receipt of such data, Biogen will provide Ionis with a [***] notice of whether Biogen still intends to exercise the Option for the applicable Collaboration Program, *provided*, *however*, that Biogen's failure to do so will not be deemed a breach of this Agreement.

3.1.2. **PoC Trial Completion Notice**. On a Collaboration Program-by-Collaboration Program basis where Ionis conducts the first PoC Trial, Ionis will provide to Biogen or its designated Affiliate (i) a copy of the most recent Investigator's Brochure for the applicable Collaboration Product, (ii) written notice from Ionis regarding completion of the first PoC Trial, and (iii) the PoC Data Package for such Collaboration Program, to the extent not already provided to Biogen under Section 3.1.1 above (such notice and package, a "***PoC Trial Completion Notice***") promptly, and in any event within [***] days after database lock for the PoC Trial for such Collaboration Program. Within 15 days of receipt of the PoC Trial Completion Notice, Biogen or an Affiliate will notify Ionis of any omissions or deficiencies that Biogen or its Affiliate believes in good faith cause the PoC Trial Completion Notice to be incomplete ("***Deficiency Notice***"). Ionis will promptly, and in any event within 15 days of receipt of the Deficiency Notice, resubmit a complete PoC Trial Completion Notice to Biogen or its designated Affiliate, including any information required to be included in the PoC Data Package that Biogen identified in the Deficiency Notice. If the Parties do not agree as to whether the PoC Trial Completion Notice is complete, the matter will be referred to the Executives for resolution. The Executives will meet promptly and negotiate in good faith to resolve the dispute and agree upon a complete PoC Trial Completion Notice.

3.1.3. **Option and Option Deadline**. On a Collaboration Program-by-Collaboration Program basis, Ionis hereby grants to Biogen and its Affiliates an exclusive option to obtain the license set forth in Section 4.1.1(a) with respect to such Collaboration Program (each an "***Option***"). Each Option for a Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program will be available to Biogen and its Affiliates until 5:00 pm (Eastern Time) on the [***] following Biogen's receipt of a complete PoC Trial Completion Notice for the applicable Collaboration Program (the "***Standard Option Deadline***"). Each Option for an ALS Collaboration Program will be available to Biogen and its Affiliates until 5:00 pm (Eastern Time) on the earlier of (A) the [***] following Biogen's receipt of the data generated under the statistical analysis plan after initial database lock for the first PoC Trial for the applicable ALS Collaboration Program, and (B) the [***] of the date a Development Candidate under such ALS Collaboration Program was designated (the "***ALS Option Deadline***"). Each Option for a Biogen Conducted Non-ALS Collaboration Program will be available to Biogen and its Affiliates until 5:00 pm (Eastern Time) on the earlier of (X) the [***] following Biogen's receipt of the data generated under the statistical analysis plan after initial database lock for the first PoC Trial for the applicable Biogen Conducted Non-ALS Collaboration Program, and (Y) the [***] of the date a Development Candidate under such Biogen Conducted Non-ALS Collaboration Program was designated (the "***Biogen Conducted Non-ALS Option Deadline***"). Notwithstanding the foregoing, if Biogen determines that an HSR Filing is required to be made under the HSR Act to exercise an Option and notifies Ionis of such determination within [***] after Biogen's receipt of the complete PoC Trial Completion Notice, the Parties will promptly file an HSR Filing in accordance with Section 3.1.4 and the Option Deadline will be extended until 5:00 pm (Eastern Time) on the fifth Business Day after the HSR Clearance Date. If, by the Option Deadline, Biogen or its designated Affiliate (i) notifies Ionis in writing that it wishes to exercise the applicable Option, and (ii) pays to Ionis the license fee set forth in Section 6.6, Ionis will, and hereby does, grant to Biogen or its designated Affiliate the license set forth in Section 4.1.1(a). If, by the Option Deadline, Biogen or its designated Affiliate has not both (y) provided Ionis a written notice stating that Biogen is exercising its Option, and (z) paid Ionis the license fee in accordance with Section 6.6, then Biogen's Option for the applicable Collaboration Program will expire and 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 under such Collaboration Program in the possession of Biogen and its contractors to the extent such data, results and information were generated by or on behalf of Biogen under this Agreement (and [***] will pay all out-of-pocket direct Third Party costs and expenses in transferring such data, results and information together with Biogen's FTE Cost in transferring such data, results and information).

3.1.4. HSR Compliance.

(a) **HSR Filing**. If Biogen notifies Ionis pursuant to Section 1.7 or Section 3.1.3 that an HSR Filing is required for Biogen to receive the license under Section 4.1.1(b) or exercise an Option under this Agreement, each of Biogen and Ionis will, within five Business Days after such notice from Biogen (or such later time as may be agreed to in writing by the Parties), file with the United States Federal Trade Commission ("***FTC***") and the Antitrust Division of the United States Department of Justice ("***DOJ***"), any HSR Filing required with respect to the transactions contemplated hereby. The Parties will cooperate with one another to the extent necessary in the preparation of any such HSR Filing. Each Party will be responsible for its own costs and expenses (other than filing fees, which Biogen will pay) associated with any HSR Filing.

(b) **HSR Clearance**. In furtherance of obtaining HSR Clearance for an HSR Filing filed under Section 3.1.4(a), Ionis and Biogen will use their respective commercially reasonable efforts to resolve as promptly as practicable any objections that may be asserted with respect to this Agreement or the transactions contemplated by this Agreement under any antitrust, competition or trade regulatory law. In connection with obtaining such HSR Clearance from the FTC, the DOJ or any other governmental authority, Biogen and its Affiliates will not be required to (i) sell, divest (including through a license or a reversion of licensed or assigned rights), hold separate, transfer or dispose of any assets, operations, rights, product lines, businesses or interest therein of Biogen or any of its Affiliates (or consent to any of the foregoing actions); or (ii) litigate or otherwise formally oppose any determination (whether judicial or administrative in nature) by a governmental authority seeking to impose any of the restrictions referenced in clause (i) above.

3.2. Changing or Adding Modalities.

3.2.1. Changing to a Collaboration Target. Provided that Biogen has complied with its diligence obligations under Section 2.1.1(c) and Section 5.1.2, at any time during the Research Term after Biogen has made the applicable payment under Section 6.2.2 with respect to a Biogen Alternate Modality Product, subject to Section 3.2.3(a), Biogen may elect to change such Biogen Alternate Modality Target to a Collaboration Target upon written notice to Ionis. Thereafter, (i) Biogen will pay Ionis the milestone payment under Section 6.2.1 (as such payment may be modified pursuant to Section 3.2.3(a)), such payment to be made within [***] days after Biogen's notice under this Section 3.2.1, (ii) Ionis will prepare and submit to the Neurology JRC an ASO Development Candidate Identification Plan for such Collaboration Target within [***] days after receipt of Biogen's notice pursuant to this Section 3.2.1, which plan will be agreed upon as provided in Section 1.10.1(a), (iii) the Parties will seek to discover and develop a Development Candidate for such target pursuant to such plan and the provisions of this Agreement and (iv) such target will no longer be a Biogen Alternate Modality Target hereunder.

3.2.2. Changing to a Biogen Alternate Modality Target. At any time during the Term after Biogen has made the applicable payment under Section 6.2.1 for a Collaboration Program, Biogen may elect to change the applicable Collaboration Target under such Collaboration Program to a Biogen Alternate Modality Target upon written notice to Ionis, in which case the provisions of Section 3.2.3(b) will apply, and as of the date of such notice, Ionis will be deemed to have granted Biogen the license under Section 4.1.1(b) with respect to such target and such target will no longer be a Collaboration Target hereunder; *provided, however*, that Biogen will not have the right to change a Collaboration Target to a Biogen Alternate Modality Target if such Collaboration Target is a Pre-Existing Target. Within [***] days of the later of (i) Ionis' receipt of Biogen's notice electing to change a particular Collaboration Target to a Biogen Alternate Modality Target, and (ii) Ionis' receipt of the data generated under the statistical analysis plan after initial database lock for any ongoing Clinical Study under the applicable Collaboration Program, by written notice to Biogen, Ionis may elect to either (1) cease all development activities under this Agreement relating to any ASO designed to bind to the applicable Biogen Alternate Modality Target (i.e., the former Collaboration Target), until otherwise permitted to conduct such development activities under Section 2.1.1(c), or (2) subject to Section 3.2.3(b), continue to develop and commercialize on its own or with a Third Party such ASOs (or any other oligonucleotides) designed to bind to the applicable Biogen Alternate Modality Target (i.e., the former Collaboration Target). If Ionis makes an election under clause (2) of this Section 3.2.2, then Section 10.4.3(d) will apply to such former Collaboration Target.

3.2.3. Economics for Changing Modalities.

(a) If, pursuant to Section 3.2.1, Biogen elects to change a Biogen Alternate Modality Target to a Collaboration Target, the provisions related to Collaboration Programs under this Agreement, including to Sections 6.2, 6.4, 6.6, 6.7, and 6.10 will apply with respect to such Collaboration Target, *provided*, *however*, that (i) if Biogen paid Ionis the milestone payment under Section 6.2.2 with respect to such target prior to the date such target changed to a Collaboration Target, then the milestone payment under Section 6.2.1 with respect to such Collaboration Target will be reduced to $[***], (ii) if Biogen paid Ionis a milestone payment under Section 6.3 with respect to such target prior to the date such target changed to a Collaboration Target, then Biogen may credit the amount of such payments against the amounts due Ionis under Sections 6.6 and, to the extent applicable, Section 6.7.

(b) If, pursuant to Section 3.2.2, Biogen elects to designate a Collaboration Target as a Biogen Alternate Modality Target, the provisions related to Biogen Alternate Modality Programs under this Agreement, including Sections 6.3 and 6.9 will apply with respect to such Biogen Alternate Modality Target; *provided*, *however*, that (i) if the Collaboration Target Biogen changed to a Biogen Alternate Modality Target was not an ALS Target, then no payment will be due under Section 6.2.2 with respect to such Biogen Alternate Modality Target and (ii) if Ionis elects to continue to develop and commercialize such oligonucleotides under clause (2) of Section 3.2.2 Biogen will not be required to pay Ionis any un-accrued milestone payments or royalties under Section 6.3 and Section 6.9 *solely* with respect to the applicable Biogen Alternate Modality Product Developed and Commercialized by Biogen as a result of its conversion to a Biogen Alternate Modality Target under Section 3.2.2.

3.2.4. Adding an Additional Modality.

3.2.4.1 Adding a Collaboration Target. Provided that Biogen has complied with its diligence obligations under Section 2.1.1(c) and Section 5.1.2, at any time during the Research Term after Biogen has made the applicable payment under Section 6.2.2 with respect to a Biogen Alternate Modality Target, Biogen may elect to add such Biogen Alternate Modality Target as a Collaboration Target upon written notice to Ionis. Thereafter, (i) Biogen will pay Ionis the milestone payment under Section 6.2.1, such payment to be made within [***] days after Biogen's notice under this Section 3.2.4.1, (ii) Ionis will prepare and submit to the Neurology JRC an ASO Development Candidate Identification Plan for such Collaboration Target within [***] days after receipt of Biogen's notice pursuant to this Section 3.2.4.1, which plan will be agreed upon as provided in Section 1.10.1(a) and the Parties will seek to discover and develop a Development Candidate for such target pursuant to such plan and the provisions of this Agreement (including, for the avoidance of doubt, the provisions of ARTICLE 6), (iii) Section 2.1.1(c) will not apply with respect to any activities conducted by Ionis pursuant to a Neurology Plan with respect to such target and (iv) Biogen may continue Developing, Manufacturing and Commercializing a Biogen Alternate Modality Product for the applicable Biogen Alternate Modality Target in accordance with the terms of this Agreement (including, for the avoidance of doubt, the provisions of ARTICLE 6).

3.2.4.2 **Adding a Biogen Alternate Modality Target**. At any time during the Term after Biogen has made the applicable payment under Section 6.2.1 for a Collaboration Program, Biogen may elect to add such Collaboration Target as a Biogen Alternate Modality Target upon written notice to Ionis; *provided, however*, that Biogen shall not have the right to add such Collaboration Target as a Biogen Alternate Modality Target if such Collaboration Target is a Pre-Existing Target. Thereafter, (a) upon Biogen's payment of the applicable milestone under Section 6.2.2, subject to Section 3.2.5, such payment to be made within [***] days after Biogen's notice under this Section 3.2.4.2, (i) Ionis will be deemed to have granted Biogen the license under Section 4.1.1(b) with respect to such target and (ii) Biogen may Develop, Manufacture and Commercialize a Biogen Alternate Modality Product for the applicable Biogen Alternate Modality Target in accordance with the terms of this Agreement (including, for the avoidance of doubt, the provisions of ARTICLE 6) and (b) the Parties will continue all activities under this Agreement with respect to the applicable Collaboration Program.

3.2.5. **HSR Compliance with Respect to Biogen Alternate Modality Targets.** If Biogen determines that an HSR Filing is required to be made under the HSR Act for Biogen to receive the license under Section 4.1.1(b) with respect to any Biogen Alternate Modality Target that is designated under Section 3.2.2 or Section 3.2.4.2 and notifies Ionis of such determination within 10 days after Biogen's notice to Ionis under such section, the Parties will promptly file an HSR Filing in accordance with Section 3.1.4 and the deadline for Biogen to pay Ionis the milestone payment (or, if applicable, a portion thereof as provided in Section 3.2.3) under Section 6.2.2 will be extended until 5:00 pm (Eastern Time) on the fifth Business Day after the HSR Clearance Date.

3.2.6. **Changes One-Time Only.** Once Biogen has elected to change a Collaboration Target to a Biogen Alternate Modality Target, or to change a Biogen Alternate Modality Target to a Collaboration Target under Section 3.2.1 or Section 3.2.2, as applicable, Biogen cannot exercise its rights under Section 3.2 to change such target back to a Collaboration Target or Biogen Alternate Modality Target, as applicable, or add such a Collaboration Target or Biogen Alternate Modality Target, as applicable, without Ionis' written consent.

3.3. Restrictions on Ionis' Right to Grant Diagnostic Rights; Right to Negotiate Diagnostic Rights.

3.3.1. On a Collaboration Product-by-Collaboration Product and Biogen Alternate Modality Product-by-Biogen Alternate Modality Product basis, Ionis hereby grants to Biogen and its Affiliates an option (the "***Diagnostic Option***") to negotiate during the Full Royalty Period or Biogen Alternate Modality Royalty Period, as applicable, the terms of an agreement under which [***]. The Diagnostic Option will be available to Biogen and its Affiliates until the expiration of the [***] or [***], as applicable, for the applicable Collaboration Product or Biogen Alternate Modality Product.

3.3.2. During the [***] or [***], as applicable, Ionis (i) has the right to [***], and (ii) will not [***].

3.3.3. If, during the [***] or [***], as applicable, Ionis grants any Third Party a [***], then Ionis will promptly notify Biogen of such [***] and will offer Biogen a [***].

ARTICLE 4.
LICENSE GRANTS

4.1. License Grants to Biogen.

4.1.1. Development and Commercialization Licenses.

(a) **Collaboration Products**. Subject to the terms and conditions of this Agreement, on a Collaboration Program-by-Collaboration Program basis, effective upon Biogen's exercise of the Option for a particular Collaboration Program in accordance with this Agreement, Ionis grants to Biogen a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize Collaboration Products under such Collaboration Program in the Field.

(b) **Biogen Alternate Modality Products**. Subject to the terms and conditions of this Agreement, on a Biogen Alternate Modality Target-by-Biogen Alternate Modality Target basis, effective upon the date Biogen pays Ionis the milestone payment under Section 6.2.2 for a particular Biogen Alternate Modality Target, Ionis grants to Biogen a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize Biogen Alternate Modality Products in the Field.

4.1.2. Sublicense Rights; CMO Licenses.

(a) Subject to the terms and conditions of this Agreement, Biogen will have the right to grant sublicenses under the licenses granted under Section 4.1.1(a) and Section 4.1.1(b) above and Section 4.4.1(b) below:

(i) under the Ionis Core Technology Patents, Ionis Product-Specific Patents and Ionis Know-How, to an Affiliate of Biogen or a Third Party; and

(ii) under the Ionis Manufacturing and Analytical Patents and Ionis 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 [***] days of first learning of any breach of such sublicense terms, Biogen 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 Ionis, Biogen hereby grants Ionis the right to enforce such sublicense terms on Biogen's behalf and will cooperate with Ionis (which cooperation will be at Biogen's sole expense and will include, Biogen joining any action before a court or administrative body filed by Ionis against such Sublicensee if and to the extent necessary for Ionis to have legal standing before such court or administrative body) in connection with enforcing such terms. Biogen will provide Ionis 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 Biogen's selecting and engaging one or more CMOs to supply Clinical Supplies under Section 4.4.1(b) or after a license is granted under Section 4.1.1, or supply API and Finished Drug Product for Commercialization, Ionis will, at Biogen's option, either (1) grant a license from Ionis to [***] under the [***] to the extent necessary for [***], which Ionis agrees it will grant to [***], or (2) permit Biogen to grant a sublicense from Biogen to [***. For Collaboration Products, each such manufacturing agreement between Biogen and a CMO will contain [***]. Biogen will provide Ionis with a true and complete copy of any manufacturing agreement entered into with a CMO within [***] days after the execution thereof. Notwithstanding the foregoing, if Ionis fails to comply with the terms of this Section 4.1.2(b) and does not cure such failure within 90 days after written notice from Biogen specifying the details of any such failure, Biogen will have the right to [***].

4.1.3. Effect of Termination on Sublicenses.

(a) If this Agreement terminates for any reason, any Sublicensee of Biogen will, from the effective date of such termination, automatically become a direct licensee of Ionis with respect to the rights sublicensed to the Sublicensee by Biogen; *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 Biogen, and (iii) such Sublicensee agrees to pay directly to Ionis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by Biogen. Biogen agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Ionis and if requested, the Sublicensee.

(b) If this Agreement terminates for any reason, any Sublicensee of Biogen under Section 4.4.2 and any Sublicensee of Ionis under Section 4.6.2 will, from the effective date of such termination, automatically become a direct licensee with respect to the rights sublicensed to the Sublicensee by the applicable Party hereunder; *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 such Sublicensee, and (iii) with respect to Sublicensees of Ionis, such Sublicensee agrees to pay directly to Biogen such Sublicensee's payments under Section 4.5.2 to the extent applicable to the rights sublicensed to it by Ionis. Each Party agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of the other Party and if requested, the Sublicensee.

4.1.4. No Implied Licenses. All rights in and to Licensed Technology not expressly licensed to Biogen under this Agreement are hereby retained by Ionis or its Affiliates. All rights in and to Biogen Technology not expressly licensed or assigned to Ionis under this Agreement, are hereby retained by Biogen or its Affiliates. Except as expressly provided in this Agreement or to perform Biogen Activities or Ionis Activities, as applicable, 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.

4.1.5. License Conditions; Limitations. Subject to Section 6.13, 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 Ionis In-License Agreements, in each case to the extent the provisions of such obligations or agreements are specifically disclosed to Biogen in writing (or via electronic data room) prior to the date the applicable license under Section 4.1.1 is granted hereunder. With respect to Collaboration Products, Ionis will disclose to Biogen any Third Party Obligations Ionis believes apply to applicable Collaboration Products each time Ionis provides (x) the [***]; (y) the [***]; and (z) the [***], and Biogen 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 Ionis written notice prior to Option exercise. If, prior to the date the applicable license under Section 4.1.1 is granted hereunder, Biogen provides Ionis with such a written notice to exclude certain Third Party Patent Rights and Know-How from such license, 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 Biogen does not provide Ionis with such a written notice to exclude such Third Party Patent Rights and Know-How prior to the date the applicable license under Section 4.1.1 is granted hereunder, 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.

4.1.6. **Trademarks for Products**. If Biogen is granted a license under Section 4.1.1 for a particular Product, to the extent that (i) Ionis owns any trademark(s) specific to such Product which Ionis used prior to the date such license was granted, and (ii) Biogen reasonably believes such trademark(s) would be necessary or useful for the marketing and sale of the applicable Product, then upon Biogen's request and at Biogen's sole cost and expense relating to such assignment, Ionis will assign its rights and title to such trademark(s) to Biogen or one or more designated Affiliates sufficiently in advance of the First Commercial Sale of the Product to enable Biogen or its Affiliates to offer such Product for sale under such trademark(s). Other than trademarks owned by Ionis prior to the date the applicable license under Section 4.1.1 is granted hereunder, Biogen or its designated Affiliate will be solely responsible for developing, selecting, searching, registering and maintaining, and, subject to Section 10.4, 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 Ionis Product-Specific Patents; Grant Back to Ionis**.

4.2.1. **Assignment to Biogen**. After Biogen has obtained the license for a particular Collaboration Program or Biogen Alternate Modality Target under Section 4.1.1 and following review and consideration by the Joint Patent Committee, Ionis will assign to Biogen or one or more of its designated Affiliates, Ionis' ownership interest in (i) all Ionis Product-Specific Patents related to such Collaboration Program or Biogen Alternate Modality Target in the Field that are owned by Ionis (whether solely owned or jointly owned with one or more Third Parties), and (ii) any Jointly-Owned Program Patents Covering Products related to such Collaboration Program or such Biogen Alternate Modality Target, and thereafter Ionis will have no further right to control any aspect of the Prosecution and Maintenance of such Ionis Product-Specific Patents and such Jointly-Owned Program Patents. The assignment of Patent Rights assigned in this Section 4.2.1 will occur within [***] days of Biogen obtaining the applicable license under Section 4.1.1.

4.2.2. **Grant Back to Ionis**. Biogen grants to Ionis a worldwide, exclusive, sublicensable license under any Ionis Product-Specific Patents and Jointly-Owned Program Patents assigned to Biogen under Section 4.2.1, (i) for all [***], (ii) to conduct its activities under other ASO Development Candidate Identification Plans and Initial Development Plans, (iii) to [***] to the extent permitted by this Agreement, (iv) to [***] to the extent permitted under APPENDIX 3, and (v) to exercise Ionis' rights under Section 2.1.1(f) (if applicable) or Section 3.2.2.

4.3. Data Licenses.

4.3.1. Data License to Biogen. Ionis hereby grants Biogen a worldwide, non-exclusive, royalty-free, sublicenseable license under any data included in the Ionis Program Know-How for (a) any use other than in connection with the development, manufacture or commercialization of an oligonucleotide and (b) use in connection with the development, manufacture or commercialization any oligonucleotide that is being developed or commercialized by the Parties under this Agreement or any Ionis/Biogen Additional Agreement.

4.3.2. Data License to Ionis. Biogen hereby grants Ionis a worldwide, non-exclusive, royalty-free, sublicenseable license under any data included in the Biogen Program Know-How solely for use in connection with the development, manufacture or commercialization of oligonucleotides to the extent permitted by this Agreement and any Ionis/Biogen Additional Agreement.

4.4. Enabling Licenses.

4.4.1. Licenses During the Option Period.

(a) Subject to the terms and conditions of this Agreement, Ionis hereby grants Biogen a worldwide, non-exclusive, sublicensable (but only as permitted in Section 4.4.2 below), royalty-free license under the Ionis Manufacturing and Analytical Know-How and Ionis Manufacturing and Analytical Patents solely to conduct Manufacturing and drug substance process and formulation development activities with respect to any Compound, Product or Collaboration Product under any Collaboration Program during the Option Period for such Collaboration Program (including the activities set forth on SCHEDULE 4.4.1(a)); *provided* that the grant of rights pursuant to this Section 4.4.1(a) shall not include the right to Manufacture any Compound, Product or Collaboration Product for Commercialization.

(b) Subject to the terms and conditions of this Agreement (including Biogen's exclusivity covenants under Section 2.1.1), [***] for Biogen to conduct any Biogen Activities that are Development activities with respect to any High Interest Target or Collaboration Target during the Option Period in accordance with this Agreement, Ionis hereby grants Biogen a worldwide, non-exclusive, sublicensable (but only as permitted in Section 4.1.2 above), royalty-free license under the Licensed Technology. Biogen will [***] arising under any Third Party agreement as a result of granting Biogen the license under this Section 4.4.1(b) within [***] days after Biogen's receipt of the applicable invoice. For clarity, the grant of rights pursuant to this Section 4.4.1(b) shall not include the right to Commercialize any such Collaboration Product or to Manufacture any such Collaboration Product for Commercialization.

4.4.2. **Biogen's Right to Sublicense.** Biogen will have the right to grant sublicenses under the license granted under Section 4.4.1(a) above (a) in the case of a sublicense of Biogen's right to conduct Manufacturing of Compounds, Products or Collaboration Products, other than any sublicense to conduct manufacturing in support of drug substance process and formulation development activities, solely to (i) [***] or (ii) [***] and (b) in the case of a sublicense of Biogen's right to conduct drug substance process and formulation development activities, including manufacturing in support thereof, to any [***]. If, within [***] days of first learning of any breach of such sublicense terms by any such Sublicensee, Biogen fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.4.2, which failure would cause an adverse effect on Ionis, Biogen hereby grants Ionis the right to enforce such sublicense terms on Biogen's behalf and will cooperate with Ionis (which cooperation will be at Biogen's sole expense and will include Biogen joining any action before or a court or administrative body filed by Ionis against such Sublicensee if and to the extent necessary to have legal standing before such court or administrative body) in connection with enforcing such terms. Biogen will provide Ionis with a true and complete copy of any sublicense granted pursuant to this Section 4.4.2 within [***] days after the execution thereof. For the avoidance of doubt, Section 4.1.3(b) shall apply to sublicenses granted under this Section 4.4.2.

4.4.3. **Enabling License to Biogen**. Subject to the terms and conditions of this Agreement (including Biogen's exclusivity covenants under Section 2.1.1), Ionis hereby grants Biogen an irrevocable, worldwide, non-exclusive, sublicenseable license under any Ionis Program Technology Controlled by Ionis or its Affiliates at any time during the Agreement Term to research, develop, manufacture, have manufactured and commercialize (a) a product that is being developed or commercialized by Biogen, its Affiliates or its Sublicensee under any Ionis/Biogen Additional Agreement other than this Agreement, and (b) products that do not include an oligonucleotide as an active pharmaceutical ingredient. Such license in clause (b) above is royalty-free; *except* that if a product being sold by Biogen, its Affiliates or Sublicensees is Covered by a Target Related Ionis Program Claim, then on a country-by-country basis Biogen will pay Ionis a royalty equal to [***]% of Net Sales of any product sold by Biogen, its Affiliates or Sublicensees so long as such product is Covered by such Target Related Ionis Program Claim in such country. A "***Target Related Ionis Program Claim***" means a Valid Claim that (i) is within an Ionis Program Patent that is solely owned by Ionis, (ii) Covers a product being sold by Biogen, its Affiliates or Sublicensee, and (iii) claims a gene target, or a method of modulating such gene target to achieve a prophylactic or therapeutic effect/benefit.

4.4.4. **Enabling License to Ionis**. Subject to the terms and conditions of this Agreement (including Ionis' exclusivity covenants under Section 2.1.1), Biogen hereby grants Ionis an irrevocable, worldwide, non-exclusive, sublicenseable license under any Biogen Program Technology Controlled by Biogen or its Affiliates at any time during the Agreement Term, other than any Biogen Results licensed to Ionis under Section 4.5.1, to research, develop, manufacture, have manufactured and commercialize products that include an oligonucleotide as an active pharmaceutical ingredient (other than products that 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 under this Agreement or any other Ionis/Biogen Additional Agreement). Such license is royalty-free; *except* that if a product being sold by Ionis, its Affiliates or Sublicensee is Covered by a Target Related Biogen Program Claim, then on a country-by-country basis Ionis will pay Biogen a royalty equal to [***]% of net sales of any product sold by Ionis, its Affiliates or Sublicensees, for so long as such product is Covered by such Target Related Biogen Program Claim in such country. For the purpose of the foregoing royalty calculation, "net sales" will be calculated [***]. The provisions of Sections 6.14.1, 6.14.2, 6.14.3, 6.15, 6.16.1, 6.16.2(a), 6.16.3 and 6.17 shall apply, *mutatis mutandis*, to any royalty payments by Ionis to Biogen under this Section 4.4.4. A "***Target Related Biogen Program Claim***" means a Valid Claim that (i) is within a Biogen Program Patent that is solely owned by Biogen, (ii) Covers a product being sold by Ionis, its Affiliates or Sublicensee, and (iii) claims a gene target, or a method of modulating such gene target to achieve a prophylactic or therapeutic effect/benefit.

4.5. **Licenses to Ionis for Biogen Results**.

4.5.1. Subject to the terms and conditions of this Agreement, Biogen hereby grants Ionis an irrevocable, worldwide, non-exclusive, sublicensable license under the Biogen Results Controlled by Biogen or its Affiliate at any time during the Agreement Term, to research, develop, make, have made, import, export, use and sell products that include an oligonucleotide as an active pharmaceutical ingredient (other than products that 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 the Parties pursuant to an Option or exclusive license granted from Ionis to Biogen under the Ionis/Biogen Additional Agreements).

4.5.2. The license granted in Section 4.5.1 shall be [***] with respect to any [***]. Such license will be [***] with respect to any [***] as follows: on a country-by-country, product-by-product and Biogen Manufacturing Program Patent-by-Biogen Manufacturing Program Patent basis, Ionis will pay Biogen [***]. If one or more Biogen Manufacturing Program Patents expires, is invalidated or otherwise ceases to Cover a product bearing royalties as set forth above, the applicable royalty rate under this Section 4.5.2 shall be recalculated to reflect the number of Biogen Manufacturing Program Patents then-Covering such product. For the purpose of the foregoing royalty calculation, [***] will be calculated as follows: [***]. If Ionis grants a sublicense under this Section 4.5 to an entity that is an Ionis Affiliate at the time Ionis grants such sublicense, such applicable sublicense will [***]. The provisions of Section 6.14 (other than Section 6.14.4), Section 6.15, Section 6.16 (other than Section 6.16.2(b)) and Section 6.17 shall apply, *mutatis mutandis*, to any royalty payments by Ionis to Biogen under this Section 4.5.2.

4.6. Right to Obtain Direct License from Biogen to Ionis Partner; Sublicensees of Ionis.

4.6.1. If requested by Ionis, Biogen shall grant a direct, [***] license under the Biogen Results to [***] on the same terms as set forth in Section 4.5 with respect to sublicenses of Ionis. Biogen shall endeavor in good faith to grant such license within [***] days of any such request by Ionis.

4.6.2. Ionis will have the right to grant sublicenses under the license granted under Section 4.5, *provided* that each such sublicense will be subject to, and consistent with, the terms and conditions of this Agreement. If, within [***] days of first learning of any breach of such sublicense terms, Ionis fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.6.2, which failure would cause an adverse effect on Biogen, Ionis hereby grants Biogen the right to enforce such sublicense terms on Ionis' behalf and will cooperate with Biogen (which cooperation will be at Ionis' sole expense and will include, Ionis joining any action before a court or administrative body filed by Biogen against such Sublicensee if and to the extent necessary for Biogen to have legal standing before such court or administrative body) in connection with enforcing such terms. Ionis will provide Biogen with a true and complete copy of any sublicense granted pursuant to this Section 4.6.2 within [***] days after the execution thereof.

4.7. Ownership of and Assistance with Regulatory Filings. If requested by Biogen, Ionis' and Biogen's regulatory teams will meet and begin to prepare a plan, which plan will be completed no later than [***] prior to such anticipated filing date, for drafting and reviewing the sections of the NDA and MAA for the applicable Collaboration Product (including establishing responsibilities for drafting and reviewing common technical document ("***CTD***") modules, authorship, plan activity timelines and associated costs and expenses) and assigning all necessary filings with any Regulatory Authority related to the applicable Collaboration Product to Biogen to ensure a smooth transition to Biogen, accelerate CTD completion and facilitate rapid NDA and MAA filing. Each CTD will be consistent with the Specific Performance Milestone Events for the applicable Collaboration Program. The Parties regulatory teams will submit such plan to the CSC, if still active. The Parties will act in good faith and mutually agree upon each such plan, *provided*, *however*, that, after exercising an Option for the applicable Collaboration Program, Biogen will have final decision making authority with respect to the [***]. Once such plan is complete, each Party will use Commercially Reasonable Efforts to execute their respective tasks and responsibilities under such plan in the time frames set forth in such plan. After exercising an Option for a particular Collaboration Program, if Biogen requests, Ionis will assist Biogen in preparing regulatory filings for the Collaboration Product, under terms negotiated in good faith between Ionis and Biogen, including payment for Ionis' time at Ionis' then applicable FTE Rate plus any reasonable out of pocket expenses incurred by Ionis in providing such assistance, utilizing the payment mechanism set forth in Section 1.14.1.

4.8. Subcontracting.

4.8.1. Subject to the terms of this Section 4.8, 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. Each Party will be responsible for any income or non-income taxes that arise as a result of such Party's use of any Third Party subcontractors hereunder, including payroll, income, withholding, sales and use, VAT, customs, duties excise or property taxes, and such taxes will not be reimbursable expenditures.

4.8.2. Ionis agrees that, where Biogen wishes to (sub)contract with a Third Party with respect to any of the rights granted under Section 4.4.1(a), Ionis shall, within [***] days of any request by Biogen, provide Biogen with a letter of authorization as necessary for Biogen to be able to contract with such Third Party in accordance with the terms of this Agreement. Biogen will ensure that any Third Party (sub)contractors Biogen uses to conduct the process development or manufacturing activities contemplated by Section 4.4.1(a) will be obligated to assign to Biogen all right, title and interest in and to any inventions developed by such (sub)contractors in the performance of such activities. For clarity, solely with respect to the Biogen Results, this Section 4.8.2 shall supersede and replace Section 7.1.3 of this Agreement to the extent of any conflict. Biogen will not enter into any new agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case that restricts, limits, diminishes or encumbers the rights granted to Ionis under the Manufacturing Process Development Terms. In addition, after the Amendment Date, Biogen will use reasonable efforts to include, in any agreement with a (sub)contractor that has substantial material obligations related to the Development, Manufacture or Commercialization of a Product, provisions requiring that, in the event the applicable Option is terminated, expires unexercised or this Agreement is terminated, such (sub)contractor would enter into an agreement with Ionis with respect to such Product that is substantially similar to such (sub)contractor's agreement with Biogen and would reasonably cooperate with Ionis to facilitate the transition of such Product to Ionis following such termination or Option expiration, including the transfer to Ionis of data and information in such (sub)contractor's possession related to the Product.

4.9. Technology Transfer.

4.9.1. Technology Transfer to Biogen during the Option Period. Within [***] days after the Amendment Date, Ionis will deliver to Biogen or one or more designated Affiliates, solely for use by Biogen, [***] to conduct any Biogen Activities that are Development activities with respect to any High Interest Target or Collaboration Target in accordance with this Agreement, all Ionis Manufacturing and Analytical Know-How in Ionis' Control [***] to conduct such Biogen Activities. If requested by Biogen, Ionis will provide Biogen with a reasonable level of assistance in connection with such transfer, which Biogen will reimburse Ionis for its time incurred in providing such assistance at the then-applicable Ionis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Ionis in providing such assistance, using the payment mechanism set forth in Section 1.14.1.

4.9.2. Technology Transfer to Biogen after Option Exercise. On a Collaboration Program-by-Collaboration Program basis, Ionis will promptly, but no later than [***] after Biogen exercises its Option for such Collaboration Program hereunder, deliver to Biogen or one or more designated Affiliates:

(a) Ionis Know-How. All Ionis Know-How in Ionis' possession that has not previously been provided hereunder, for use solely in accordance with the licenses granted under Section 4.1.1 and Section 10.4.2, and Ionis will and does hereby assign to Biogen all of Ionis' right, title and interest in and to the IND for the applicable Development Candidate, together with all Regulatory Materials (including drafts) that relate to the applicable Development Candidate; *provided that*, (x) notwithstanding the foregoing, and subject to the provisions of Section 2.1, the Parties acknowledge that Ionis shall be permitted to use excerpts or portions of any such assigned Regulatory Materials in any other regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction related to products other than the Development Candidate, *provided, further that* such excerpts or portions shall not include (i) any non-public data or information, in each case, related solely to the applicable Development Candidate, or (ii) any Confidential Information of Biogen, and (y) for clarity, such assignment of Ionis' right, title and interest in and to such Regulatory Materials shall not include the assignment of any Know-How (including any data) contained therein. If Ionis intends to use any excerpt or portion of any such assigned Regulatory Materials in accordance with clause (x) of the preceding sentence that are not in the public domain and do not relate to Ionis' antisense oligonucleotide platform, Ionis shall, at least [***] days in advance of the anticipated submission of such excerpt or portion to a Regulatory Authority, notify Biogen of such intent and provide to Biogen a copy of such proposed excerpt or portion for review and comment. The Parties shall discuss in good faith any comments of Biogen with respect to such proposed excerpt or portion prior to submission thereof. To assist with the transfer and assignment of such Ionis Know-How, Ionis will make its personnel reasonably available to Biogen during normal business hours for up to [***] ([***]) of Ionis' time for each Collaboration Program to transfer such Ionis Know-How under this Section 4.9.2(a). Thereafter, if requested by Biogen, Ionis will provide Biogen with a reasonable level of assistance in connection with such transfer, which Biogen will reimburse Ionis for its time incurred in providing such assistance at the then-applicable Ionis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Ionis in providing such assistance, using the payment mechanism set forth in Section 1.14.1.

(b) **Ionis Manufacturing and Analytical Know-How**. Solely for use by Biogen, its Affiliates or a Third Party acting on Biogen's behalf to Manufacture API in Biogen's own or an Affiliate's manufacturing facility, all Ionis Manufacturing and Analytical Know-How in Ionis' Control relating to applicable Products, which is necessary for the exercise by Biogen, its Affiliates or a Third Party of the Manufacturing rights granted under Section 4.1.1(a). Upon Biogen's request, subject to Section 4.1.2, Ionis will provide up to [***] for [***] ([***]) of its time for each Collaboration Program to transfer such Ionis Manufacturing and Analytical Know-How under this Section 4.9.2(b) to any Third Party Manufacturing API, Clinical Supplies or Finished Drug Product on Biogen's behalf solely to Manufacture API, Clinical Supplies or Finished Drug Product in accordance with the terms of this Agreement. Thereafter, if requested by Biogen, Ionis will provide Biogen with a reasonable level of assistance in connection with such transfer, which Biogen will reimburse Ionis for its time incurred in providing such assistance at the then-applicable Ionis FTE Rate, plus any reasonable out-of-pocket expenses incurred by Ionis in providing such assistance, using the payment mechanism set forth in Section 1.14.1.

(c) **API and Product**. Upon Biogen's written request, Ionis will sell to Biogen any bulk API, Clinical Supplies and Finished Drug Product in Ionis' possession at the time of Option exercise, at a price equal to [***].

(d) **Trial Master File**. Upon Biogen's written request, Ionis will provide to Biogen or its designated Affiliate a copy of Ionis' trial master file for such Collaboration Program (such trial master file, the "***Trial Master File***") promptly, and in any event within [***] days after Ionis' receipt of such written request. Within [***] days after receipt of the Trial Master File, Biogen or an Affiliate may notify Ionis of any omissions or deficiencies that Biogen or its Affiliate believes in good faith cause the Trial Master File to be incomplete (such notice, a "***Trial Master File Deficiency Notice***"). Ionis will promptly, and in any event within [***] days after receipt of the Trial Master File Deficiency Notice, resubmit a complete Trial Master File to Biogen or its designated Affiliate, including any information required to be included in a Trial Master File that Biogen requests be included in the Trial Master File. If the Parties do not agree as to whether the Trial Master File is complete, the matter will be referred to the Executives for resolution. The Executives will meet promptly and negotiate in good faith to resolve the dispute and agree upon a complete Trial Master File. If Ionis is the Commercializing Party of a Discontinued Collaboration Product, this Section 4.9.2(d) will apply to such Discontinued Collaboration Product *mutatis mutandis* such that Biogen will transfer to Ionis Biogen's trial master file for such Discontinued Collaboration Product.

4.9.3. Results.

(a) Each Party shall share with the other Party on an Annual basis (preferably at in-person meetings) the results of such Party's manufacturing process development activities, including all data, the identity and location of vendors, information and results received from vendors, and planned additional work, (a) in the case of Biogen, to the extent arising under the Manufacturing Process Development Terms (all Know-How and Patent Rights within the foregoing, the "***Biogen Results***") and (b) in the case of Ionis, to the extent arising under or otherwise subject to a disclosure obligation of Ionis under this Agreement, (all Know-How and Patent Rights within the foregoing, the "***Ionis Results***" and, collectively with the Biogen Results, the "***Results***"). All intellectual property matters with respect to the Results, including any Patent Rights therein, will be governed by the intellectual property provisions of this Agreement, and the Know-How and Patent Rights included in the Ionis Results shall constitute Ionis Manufacturing and Analytical Know-How and Ionis Manufacturing and Analytical Patent Rights, respectively, under this Agreement. If requested by either Party, Biogen and Ionis will establish a manufacturing committee to facilitate the exchange of Results between the Parties. For clarity, Biogen shall have the right, in its sole discretion, to determine whether to seek patent protection for any Biogen Results that are not jointly owned with Ionis, and Biogen shall control and be responsible for all aspects of the Prosecution and Maintenance of any Patent Right within such Biogen Results (each, a "***Biogen Manufacturing Program Patent***") in accordance with Section 7.2.2(c) of this Agreement. Biogen shall notify Ionis within [***] days if Biogen files a patent application Controlled by Biogen or its Affiliates that claims any Biogen Results and shall provide Ionis with a copy of such patent application. Ionis will have no obligation to incorporate any Biogen Results into Ionis' manufacturing processes.

(b) For clarity, the Manufacturing Process Development Terms, and not the enabling licenses set forth in Section 4.4.3 and Section 4.4.4, shall govern with respect to all Results.

ARTICLE 5.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1. Biogen Diligence.

5.1.1. Collaboration Products.

(a) Prior to Option exercise, Biogen will use Commercially Reasonable Efforts to conduct (i) any Biogen Activities on the timeline set forth in the applicable Neurology Plan, (ii) except as provided under Section 1.10.2(c)(ii), for each ALS Collaboration Program all activities under each Initial Development Plan on the timeline set forth in the applicable Initial Development Plan, and (iii) except as provided under Section 1.10.2(c)(ii) and Section 1.10.4(a), for each Biogen Conducted Non-ALS Collaboration Program all activities under each Initial Development Plan on the timeline set forth in the applicable Initial Development Plan. Without limiting the foregoing, Biogen may discontinue Development under such an Initial Development Plan if after having consulted, and having given good faith consideration to the recommendations of the Neurology JDC and a mutually-agreed Third Party expert, Biogen in good faith believes that continuing such Development would (1) pose an unacceptable risk or threat of harm in humans, or (2) violate any Applicable Law, ethical principles, or principles of scientific integrity, in which case Biogen will provide Ionis with reasonable advance notice of such discontinuation, including the grounds for Biogen's determination, and Section 10.4.3 will apply.

(b) Following an Option exercise, Biogen 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 Biogen will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize at least one Product from each Collaboration Program for which an Option has been exercised.

5.1.2. Biogen Alternate Modality Products. Following the date a license is granted to Biogen under Section 4.1.1(b) for a particular Biogen Alternate Modality Product, Biogen 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 Biogen Alternate Modality Products; and Biogen will use Commercially Reasonable Efforts to develop, manufacture and commercialize at least one Biogen Alternate Modality Product for each Biogen Alternate Modality Target.

5.1.3. Multi-Indication Targets for Non-Neurological Indications. Without limiting any of the foregoing, with respect to any plan for the development and commercialization of a Multi-Indication Target Biogen has agreed to conduct pursuant to a plan mutually-agreed under APPENDIX 3, Biogen will use Commercially Reasonable Efforts to develop, manufacture and commercialize at least one Product for such Multi-Indication Target in accordance with such agreed plan.

5.1.4. **Specific Performance Milestone Events for Collaboration Products**. Without limiting any of the foregoing, (i) following an Option exercise for Collaboration Programs that are not ALS Collaboration Programs, and (ii) following the designation of the Development Candidate for ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs, Biogen will use Commercially Reasonable Efforts to achieve the specific performance milestone events set forth in SCHEDULE 5.1.4, as such schedule may be updated from time to time in accordance with Section 1.10.2(d) ("***Specific Performance Milestone Events***") for a Collaboration Product on the timeline set forth in SCHEDULE 5.1.4; *provided, however*, [***].

5.1.5. **Development Results under ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs**. Without limiting the other provisions of this Agreement, promptly following its generation or receipt of the results of a [***] or a Clinical Study under an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, as applicable, Biogen will provide Ionis (i) all study reports from [***] studies for the applicable Collaboration Product that are intended to support an investigational new drug application, (ii) all study reports for any pre-clinical and clinical trials conducted by Biogen for such Collaboration Product, (iii) the data generated under the [***] for the applicable PoC Trial(s), and (iv) copies of all filings submitted to Regulatory Authorities regarding such Collaboration Product.

5.1.6. **Integrated Development Plan for Products**. On a Product-by-Product basis, Biogen will prepare a Development and global integrated Product plan outlining key aspects of the Development of each Product through Approval as well as key aspects of worldwide regulatory strategy, market launch, and Commercialization, including Product sales forecasts (each, an "***Integrated Development Plan***" or "***IDP***"). Biogen will prepare the IDP no later than (i) [***] after Option exercise for a Collaboration Product or (ii) after the First Commercial Sale of a Biogen Alternate Modality Product, and the IDP will include information consistent in scope and content with the information Biogen's senior management uses for internal decision-making for such Product. SCHEDULE 5.1.6 sets forth examples of the types of information Biogen expects will be available to include in the IDP at different stages of development and commercialization. Once Biogen has prepared such plans, Biogen will update the IDP consistent with Biogen's standard practice and provide such updates to the CSC [***] (or Ionis after the CSC terminates under Section 1.18.5). Biogen and Ionis will meet [***] basis to discuss the draft of the IDP and Biogen will consider, in good faith, any proposals and comments made by the CSC (or Ionis after the CSC terminates under Section 1.18.5) for incorporation in the final IDP. Notwithstanding the foregoing, Biogen's obligations to provide Ionis with information or reports with respect to a Product under this Section 5.1.6 will terminate if [***].

5.1.7. **Investigator's Brochure for Collaboration Products**. After Option exercise, Ionis will provide to Biogen an up-to-date version of the Investigator's Brochure for the applicable Collaboration Product. Biogen will keep Ionis reasonably informed with respect to the status, activities and progress of Development of Collaboration Products by providing updated versions of the Investigator's Brochure for each Collaboration Product to Ionis [***] and when Development of such Collaboration Product results in any substantive change to the safety or risk to the Collaboration Product. Biogen's obligations under this Section 5.1.7 will terminate with respect to a Collaboration Product if [***].

5.1.8. **Applicable Laws**. Biogen will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

5.2. **Regulatory Matters; Global Safety Database; Pharmacovigilance Agreement**.

5.2.1. **IND-Holder**. Subject to this Section 5.2, for Collaboration Programs that are not ALS Collaboration Programs or Biogen Conducted Non-ALS Collaboration Programs, Ionis will be the IND-holder and will be responsible for all communications with Regulatory Authorities regarding such Collaboration Programs prior to the applicable Option exercise. Subject to this Section 5.2, for ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs, Biogen will be the IND-holder and will be responsible for all communications with Regulatory Authorities regarding such ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs. Biogen will be the IND-holder after the applicable Option exercise for each Collaboration Program in accordance with Section 3.1.3, and, except as otherwise provided in this Section 5.2, shall thereafter have sole decision-making authority with respect to the matters set forth in this Section 5.2.

5.2.2. **Pharmacovigilance Agreement**. As soon as reasonably practicable following designation of a particular Development Candidate, and in any event no later than [***] prior to the date on which Ionis or Biogen anticipates filing an IND for the associated Collaboration Product with a Regulatory Authority, the Parties will enter into a Safety Drug Exchange Agreement relating to the collection, review, assessment, tracking, exchange and filing of information related to adverse events associated with such Collaboration Product occurring prior to the First Commercial Sale in any country on terms substantially the same as the terms of the Safety Drug Exchange Agreement to be entered into by the Parties with respect to adverse events associated with products developed under the Ionis/Biogen Additional Agreements. In addition, following the Amendment Date the Parties will discuss in good faith the possibility of entering into a single Safety Drug Exchange Agreement with respect to all activities under this Agreement and the Ionis/Biogen Additional Agreements. No later than [***] days prior the date on which Biogen reasonably anticipates that it will exercise an Option, Biogen will so notify Ionis and the pharmacovigilance departments of each of Ionis and Biogen will meet and determine the approach to be taken for the collection, review, assessment, tracking, exchange and filing of information related to adverse events associated with the applicable Collaboration Product occurring after such First Commercial Sale, consistent with the provisions of this Section 5.2. Such approach will be documented in a separate and appropriate written pharmacovigilance agreement between the Parties which will control with respect to the subject matter covered therein (the "***Pharmacovigilance Agreement***"). Such agreement will specify that the owner of the IND for a Collaboration Product will be the global commercial safety database owner for such Collaboration Product with primary responsibility for maintaining such database, and that Ionis will be and remain the owner of the Ionis Internal ASO Safety Database with primary responsibility for maintaining such database. Such agreement will also specify that, prior to Biogen's exercise of the applicable Option, the Parties will communicate updates on safety data regarding a Collaboration Product to Biogen through monthly telephone calls between the drug safety representatives of Biogen and Ionis. Biogen and Ionis will jointly review and discuss safety issues arising under any Collaboration Program that may have implications on any Initial Development Plan for such Collaboration Program. Biogen may suggest actions to address Collaboration Product safety data or audit findings, and Ionis will consider all such suggestions in good faith. The Pharmacovigilance Agreement will be in accordance with, and will enable the Parties and their Affiliates or licensees or Sublicensees, as applicable, to fulfill, local and international regulatory reporting obligations to Regulatory Authorities and other Applicable Law.

5.2.3. **Regulatory Communications Regarding Clinical Study Trial Designs**.

(a) The Party who is the IND-holder will not initiate discussions with a Regulatory Authority regarding the [***] for a Collaboration Program until such [***] have been established pursuant to Section 1.10.2(d), as applicable.

(b) With respect to a Collaboration Program, to the extent practical, prior to any scheduled meeting with a Regulatory Authority regarding the [***] for such Collaboration Program, (i) the applicable Neurology JDC (or the Parties, if Ionis ceases its participation in such Neurology JDC under Section 1.18.5) will discuss and mutually agree upon the approximate timing and objectives for such meeting and (ii) the Party who is the IND-holder will provide the other Party with (A) an invitation to attend at least [***] and (B) an [***] with the IND-holder. In addition, the IND-holder will allow the other Party to participate in any such meeting under the direction of The IND-holder *provided, however*, that the IND-holder may exclude such other Party from any portion of such meeting that does not pertain to such Collaboration Program.

(c) With respect to a Collaboration Program, in each case, to the extent regarding the [***] for such Collaboration Program, the Party who is the IND-holder will promptly provide the other Party with (i) final copies of all material correspondence with and submission to any Regulatory Authority promptly following submission thereof, (ii) a [***] from a Regulatory Authority, and (iii) a [***] with a Regulatory Authority.

(d) With respect to a Collaboration Program, the Party who is the IND-holder will provide the other Party with [***] any Regulatory Authority that materially impact the [***] for such Collaboration Program sufficiently [***] to the applicable Regulatory Authority to enable the other Party to have a meaningful [***] thereof. The [***] any Regulatory Authority must reflect the Initial Development Plan. The applicable Neurology JDC (or the Parties if Ionis ceases its participation in such Neurology JDC under Section 1.18.5) will [***] on the [***]; *provided* that if [***] prior to a Regulatory Authority's requirement for a response as determined by [***] will consider in good faith [***].

5.2.4. **Participation in Regulatory Meetings for Collaboration Products**. With respect to a Collaboration Program, each Party will provide the other Party with as much advance written notice as practicable of any meetings that such first Party has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Collaboration Product under such Collaboration Program or that directly relate to Ionis' antisense oligonucleotide chemistry platform, and will allow two representatives of the other Party to participate in any such meetings under the direction of such first Party; *provided, however*, that, if such first Party is Ionis, Ionis may exclude Biogen from any portion of such meeting that does not pertain to such Collaboration Product; and *provided, further*, that, if such first Party is Biogen, Biogen may exclude Ionis from any portion of such meeting that does not pertain to such Collaboration Product or to Ionis' antisense oligonucleotide chemistry platform.

5.2.5. **Regulatory Communications for Collaboration Products**. With respect to a Collaboration Program, each Party will promptly provide the other Party with copies of documents and communications submitted to (including drafts thereof) and received from Regulatory Authorities [***] that materially impact the Development or Commercialization of Collaboration Products under such Collaboration Program for such other Party's review and comment, and such first Party will consider in good faith including any comments provided by such other Party to such documents and communications. Each Party will promptly notify the other Party upon receipt of any such documents or communications from any Regulatory Authority [***].

5.2.6. **Class Generic Claims for Collaboration Products**. To the extent Biogen intends to make any claims in a Collaboration Product label or regulatory filing that are class generic to ASOs, Biogen will provide such claims and regulatory filings to Ionis in advance and will consider in good faith any proposals and comments made by Ionis, *provided, however*, that Biogen is not obligated to incorporate such proposals and comments in any such claims and regulatory filings.

5.2.7. Ionis' Antisense Safety Database.

(a) Ionis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during pre-clinical and clinical development (the "***Ionis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Ionis compounds, Biogen will cooperate in connection with populating the Ionis Internal ASO Safety Database. To the extent collected by Biogen and in the form in which Biogen uses/stores such information for its own purposes, Biogen will provide Ionis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Collaboration Product as soon as practicable following the date such information is available to Biogen (but not later than [***] days after Biogen's receipt of such information). In connection with any reported serious adverse event, Biogen will provide Ionis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Collaboration Product, Biogen will provide Ionis with copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within [***] days following the date such information is filed or is available to Biogen, as applicable. Furthermore, Biogen will promptly provide Ionis with any supporting data and answer any follow-up questions reasonably requested by Ionis. All such information disclosed by Biogen to Ionis will be Biogen Confidential Information; *provided*, *however*, that Ionis may disclose any such Biogen Confidential Information to (i) Ionis' other partners pursuant to Section 5.2.7(b) below if such information is regarding class generic properties of ASOs, or (ii) any Third Party, in each case, so long as Ionis does not disclose the identity of a Collaboration Product or Biogen. Biogen will deliver all such information to Ionis for the Ionis Internal ASO Safety Database to Ionis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Ionis). Biogen will also cause its Affiliates and Sublicensees to comply with this Section 5.2.7(a).

(b) From time to time, Ionis utilizes the information in the Ionis Internal ASO Safety Database to conduct analyses to keep Ionis and its partners informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Ionis identifies safety or other related issues that may be relevant to a Collaboration Product (including any potential class-related toxicity), Ionis will promptly (and in no event later than five Business Days following identification by Ionis) inform Biogen of such issues and, if requested, provide the data supporting Ionis' conclusions.

5.3. **Research and Manufacturing Records**. Each Party shall maintain, consistent with its then-current internal policies and practices, and cause its employees and subcontractors to maintain, consistent with its internal policies and Applicable Law, for at least ten years, records and laboratory notebooks, inventory, purchase and invoice records and Manufacturing records in each case with respect to the Collaboration Products in sufficient detail and in a good scientific manner appropriate for (i) inclusion in filings with Regulatory Authorities for such Collaboration Products, and (ii) obtaining and maintaining intellectual property rights and protections, including Patent Rights for such Collaboration Products. Such records and laboratory notebooks shall be complete and accurate in all material respects and shall fully and properly reflect all work done, data and developments made, and results achieved. Each Party shall allow the other Party, to the extent necessary for such regulatory or intellectual property protection purposes, to inspect or copy such records, subject to redaction by such Party.

5.4. **Product Development Plans for ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs**. With respect to each ALS Collaboration Program and each Biogen Conducted Non-ALS Collaboration Program, Biogen shall propose and develop a product development plan, which shall govern CMC-related matters for the applicable Collaboration Product. Ionis shall have the opportunity to review and comment on each such product development plan and Biogen shall consider any such comments in good faith.

ARTICLE 6.
FINANCIAL PROVISIONS

6.1. **Up-Front Fee**. Within five Business Days following the Effective Date, Biogen will pay Ionis an up-front fee of $100,000,000.

6.2. **Drug Discovery Milestone Payments**.

6.2.1. **Collaboration Targets**. For each Collaboration Program, after (a) a Collaboration Target is designated under this Agreement, and (b) Ionis begins designing human development candidates under such Collaboration Program for human candidate screening under the applicable ASO Development Candidate Identification Plan ([***]), Ionis will so notify Biogen (such notice, the "***Design Notice***") and Biogen will pay Ionis a milestone payment equal to (i) $[***] for Collaboration Programs that are not ALS Collaboration Programs [***], subject to any applicable credits permitted by Section 1.8.3 or Section 1.8.4, (ii) $[***] for ALS Collaboration Programs [***], or (iii) $[***].

6.2.2. **Biogen Alternate Modality Targets**. On a Biogen Alternate Modality Target-by-Biogen Alternate Modality Target basis, each time a Neurology Target is designated a Biogen Alternate Modality Target under this Agreement, Biogen will pay Ionis a milestone payment equal to $[***], subject to any applicable credits permitted by Section 1.8.3 or Section 1.8.4.

6.3. **Milestone Payments for Achievement of Milestone Events by Biogen Alternate Modality Products**. Subject to Section 3.2.3(b), for each Biogen Alternate Modality Target, Biogen will pay to Ionis the milestone payments as set forth in TABLE X below when a milestone event (each, a "***Biogen Alternate Modality Milestone Event***") listed in TABLE X is first achieved by a Biogen Alternate Modality Product related to such Biogen Alternate Modality Target:

TABLE X	
Biogen Alternate Modality Milestone Event	Milestone Event Payment per Biogen Alternate Modality Target
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]
[***]	$[***]

6.4. **Non-ALS Collaboration Program Milestone Payments for Achievement of Pre-Licensing Milestone Events**. As further consideration for Biogen's Options, on a Collaboration Program-by-Collaboration Program basis where such a Collaboration Program is not an ALS Collaboration Program, Biogen will pay to Ionis the milestone payments as set forth in TABLE 1 below when a milestone event (each, a "***Standard Pre-Licensing Milestone Event***") listed in TABLE 1 is first achieved by a Collaboration Product under such Collaboration Program:

TABLE 1		
Standard Pre-Licensing Milestone Event	Milestone Event Payment per Collaboration Program that is not an ALS Collaboration Program or Biogen Conducted Non-ALS Collaboration Program	Milestone Event Payment per Biogen Conducted Non-ALS Collaboration Program
[***]	$[***]	$[***]
[***]	[***]	$[***]
[***]	[***]	$[***]

On a Collaboration Program-by-Collaboration Program basis, where such a Collaboration Program is not an ALS Collaboration Program, Biogen will pay to Ionis the Milestone Event payments as set forth in TABLE 1 after the applicable Milestone Event is first achieved by a Collaboration Product under such Collaboration Program, even if Biogen has exercised the applicable Option prior to achievement of the Milestone Event; *provided*, *however*, that if Biogen exercises the Option prior to achievement of the [***] Milestone Event, then the milestone payment for achievement of the [***] Milestone Event will be reduced to $[***].

6.5. **ALS Collaboration Program Milestone Payments for Achievement of Pre-Licensing Milestone Events**. As further consideration for Biogen's Options, on an ALS Collaboration Program-by-ALS Collaboration Program basis, Biogen will pay to Ionis the milestone payments as set forth in TABLE 2 below when a milestone event (each, an "***ALS Pre-Licensing Milestone Event***") listed in TABLE 2 is first achieved by a Collaboration Product under such a Collaboration Program. Subject to the penultimate paragraph of Section 6.7, the amount of the payment for such Milestone Events will be determined based on whether or not such ALS Collaboration Program is a [***] Collaboration Program:

TABLE 2

ALS Pre-Licensing Milestone Event	Column 1 Milestone Event Payment per ALS Collaboration Program that is *not* a [***] Collaboration Program [***]	Column 2 Milestone Event Payment per [***] Collaboration Program	Column 3 Milestone Event Payment for the [***]
[***]	$[***]	$[***]	[***]
[***]	$[***]	$[***]	[***]
[***]	$[***]	$[***]	[***]
[***]	[***]	[***]	$[***]
[***]	$[***]	$[***]	$[***]

On an ALS Collaboration Program-by-ALS Collaboration Program basis, Biogen will pay to Ionis the Milestone Event payments as set forth in TABLE 2 after the applicable Milestone Event is first achieved by a Collaboration Product under such an ALS Collaboration Program, even if Biogen has exercised the applicable Option prior to achievement of the Milestone Event.

6.6. **License Fee**. On an Option-by-Option basis, together with Biogen's written notice to Ionis stating that Biogen is exercising such Option in accordance with this Agreement, Biogen will pay to Ionis a license fee of (A) $[***] for any Collaboration Program [***]; *provided*, *however*, that if (i) Biogen exercises the Option prior to the [***], the license fee for such Option will be [***] or (ii) Biogen exercises the Option to a [***] Collaboration Program, subject to the last paragraph of Section 6.7, the license fee for such Option will be [***], or (B) $[***]; *provided*, *however*, that if Biogen exercises the Option prior to the [***], the license fee for such Option will be [***]. If Biogen notifies Ionis that it desires to exercise an Option prior to the [***], then the Parties will discuss and negotiate in good faith.

6.7. **Milestone Payments for Achievement of Post-Licensing Milestone Events**. On a Collaboration Program-by-Collaboration Program basis, Biogen will pay to Ionis the milestone payments as set forth in TABLE 3 below when a milestone event (each, a "***Post-Licensing Milestone Event***") listed in TABLE 3 is first achieved by a Collaboration Product under such Collaboration Program, where (subject to the last paragraph of Section 6.7) the amount of the payment for such Milestone Event will be determined based on whether or not such Collaboration Program is a [***] Collaboration Program:

TABLE 3		
Post-Licensing Milestone Event	Column 1 Milestone Event Payment per Collaboration Program that is *not* a [***] Collaboration Program	Column 2 Milestone Event Payment per [***] Collaboration Program
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]

On a Collaboration Program-by-Collaboration Program basis, if Biogen exercises an Option for a Collaboration Program that is not a [***] Collaboration Program, prior to the [***], Biogen will pay to Ionis [***] upon the earlier of (a) [***] or (b) [***]. For the avoidance of doubt, if such $[***] payment is paid pursuant to clause (b) of the preceding sentence, such payment will be in addition to the amount due upon the occurrence of the corresponding Post-Licensing Milestone Event under TABLE 3 above.

If, with respect to a particular [***] Collaboration Program, Biogen Initiates a Phase 2 Trial in an indication other than [***] (e.g., [***] or a [***] indication) Biogen will pay Ionis [***] within [***] days of the Initiation of such Phase 2 Trial.

If, with respect to a particular [***] Collaboration Program, Biogen Initiates a Phase 3 Trial or files for Approval in an indication other than [***] (e.g., [***] or a [***] indication) such Collaboration Program will thereafter be a Collaboration Program (and not a [***] Collaboration Program) under this Agreement, and Biogen will pay Ionis (i) $[***] and (ii) [***] within [***] days of the Initiation of such Phase 3 Trial or filing for Approval.

6.8. Limitations on Milestone Payments; Exceptions; Notice.

6.8.1. On a Collaboration Product-by-Collaboration Product basis, the [***] milestone payment in TABLE 3 is creditable against the first Milestone Event payment for [***]. For example, if the [***] Milestone Event is achieved by a Collaboration Product in the United States, then the milestone payment for such Milestone Event is creditable against the first to occur of the (i) [***] (ii) [***] or (iii) [***] milestone payments for such Collaboration Product.

6.8.2. On a Biogen Alternate Modality Target-by-Biogen Alternate Modality Target basis, each milestone payment set forth in TABLE X above will be paid only once upon the first achievement of the Milestone Event regardless of how many Biogen Alternate Modality Products related to such Biogen Alternate Modality Target achieve such Milestone Event.

6.8.3. On a Collaboration Program-by-Collaboration Program basis, each milestone payment set forth in TABLE 1, TABLE 2 and TABLE 3 above will be paid only once upon the first achievement of the Milestone Event regardless of how many Collaboration Products under such Collaboration Program achieve such Milestone Event.

6.8.4. If a particular 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 a later Milestone Event the Milestone Event payment applicable to such earlier 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. Similarly, if a Party proceeds directly to [***] without achieving the [***] then upon achieving the [***] Milestone Event, both the [***] and [***] Milestone Event payments are due. If Biogen [***] for a Biogen Alternate Modality Product, then both the [***] milestone payment and the [***] milestone payment will be due upon [***].

6.8.5. Each time a Milestone Event is achieved under this ARTICLE 6, Biogen will send Ionis, or Ionis will send Biogen, as the case may be, a written notice thereof promptly (but no later than five Business Days) following the date of achievement of such Milestone Event and such payment will be due within [***] days of the date such notice was delivered.

6.8.6. With respect to the [***] Collaboration Program for [***], except as expressly set forth in Section 6.5, the milestone payments and license fees set forth in Section 6.5, Section 6.6 and Section 6.7 for [***] Collaboration Programs that are not [***] Collaboration Programs shall apply with respect to such [***] Collaboration Program. For clarity, the provisions of the Neurology Drug Discovery and Development Collaboration, Option and License Agreement between Ionis and Biogen, dated as of December 10, 2012, as such agreement may be amended from time to time, shall not apply with respect to the [***] Collaboration Program for [***].

6.9. Royalty Payments to Ionis for Biogen Alternate Modality Products.

6.9.1. Royalties for Biogen Alternate Modality Products. As partial consideration for the rights granted to Biogen hereunder, subject to the provisions of Section 3.2.3(b) and Section 6.9.2, Biogen will pay to Ionis a [***]% royalty on Annual worldwide Net Sales of Biogen Alternate Modality Products sold by Biogen, its Affiliates or Sublicensees, on a country-by-country basis (the "***Biogen Alternate Modality Royalty***").

6.9.2. Royalty Period for Biogen Alternate Modality Products. Biogen's obligation to pay Ionis the Biogen Alternate Modality Royalty above with respect to a Biogen Alternate Modality Product will continue on a country-by-country and Biogen Alternate Modality Product-by-Biogen Alternate Modality Product basis from the date of First Commercial Sale of such Biogen Alternate Modality Product until the [***] anniversary of the First Commercial Sale of such Biogen Alternate Modality Product in such country (such royalty period, the "***Biogen Alternate Modality Royalty Period***"); *provided*, that Biogen will pay [***] (if applicable) for as long as Biogen, its Affiliates or Sublicensees are selling Biogen Alternate Modality Products.

(a) Biogen will pay Ionis royalties on Net Sales of Biogen Alternate Modality Products arising from named patient and other similar programs under Applicable Laws, and Biogen will provide reports and payments to Ionis consistent with Section 6.14.

(b) No royalties are due on Net Sales of Biogen Alternate Modality Products arising from compassionate use and other programs providing for the delivery of Biogen Alternate Modality Product at no cost.

(c) The sales of Biogen Alternate Modality Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Biogen Alternate Modality Royalty Period.

6.10. Royalty Payments to Ionis for Collaboration Products.

6.10.1. Biogen Full Royalty for Collaboration Products. As partial consideration for the rights granted to Biogen hereunder, subject to the provisions of this Section 6.10.1 and Section 6.10.2, Biogen will pay to Ionis royalties on a Collaboration Program-by-Collaboration Program basis, on Annual worldwide Net Sales of Collaboration Products included in the applicable Collaboration Program sold by Biogen, its Affiliates or Sublicensees, on a country-by-country basis, in each case in the amounts as follows in TABLE 4 below (the "***Biogen Full Royalty***"):

TABLE 4		
Royalty Tier	**Annual Worldwide Net Sales of Collaboration Products for the applicable Collaboration Program**	**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 ≥ $[***] but < $[***]	[***]%
4	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%

Annual worldwide Net Sales of Collaboration Products will be calculated by [***].

(a) Biogen will pay Ionis royalties on Net Sales of Collaboration Products arising from named patient and other similar programs under Applicable Laws, and Biogen will provide reports and payments to Ionis consistent with Section 6.14. No royalties are due on Net Sales of Collaboration Products arising from compassionate use and other programs providing for the delivery of Collaboration Product at no cost. The sales of Collaboration Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Full Royalty Period.

(b) For purposes of clarification, any Ionis Product-Specific Patents assigned to Biogen as set forth in Section 4.2.1 will still be considered Ionis Product-Specific Patents for determining the royalty term and applicable royalty rates under this ARTICLE 6.

(c) For clarity, the provisions of this Section 6.10 shall apply to Net Sales of Collaboration Products under the [***] Collaboration Program for [***], and the provisions of the Neurology Drug Discovery and Development Collaboration, Option and License Agreement between Ionis and Biogen, dated as of December 10, 2012, as such agreement may be amended from time to time, shall not apply.

6.10.2. Application of Royalty Rates for Collaboration Products. All royalties set forth under Section 6.10.1 are subject to the provisions of this Section 6.10.2, and are payable as follows:

(a) **Full Royalty Period for Collaboration Products**. Biogen's obligation to pay Ionis the Biogen Full Royalty above with respect to a Collaboration Product will continue on a country-by-country and Collaboration Product-by-Collaboration Product basis from the date of First Commercial Sale of such Collaboration Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents Covering such Collaboration Product in the country in which such Collaboration Product is made, used or sold, (ii) the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Collaboration Product (e.g., such as in the case of an orphan drug), or (iii) the [***] anniversary of the First Commercial Sale of such Collaboration Product in such country (such royalty period, the "***Full Royalty Period***").

(b) **Competition from Generic Products for Collaboration Products**. Subject to Section 6.11, on a country-by-country and Collaboration Product-by-Collaboration Product basis, if, within the [***], a Generic Product is sold in a country, then the Biogen Full Royalty rate used to pay Ionis royalties on such Collaboration Product in such country will be reduced to [***]% of the otherwise applicable Biogen Full Royalty rate. For the purpose of determining the [***] for a particular Collaboration Product under this Section 6.10.2(b), if requested by Biogen, Ionis and Biogen will meet and confer and mutually agree upon the Parties' best estimate of when the Full Royalty Period [***] in each country where Collaboration Products are being sold.

(c) **Reduced Royalty Period for Collaboration Products**. Subject to Section 6.11, on a country-by-country and Collaboration Product-by-Collaboration Product basis, after the expiration of the Full Royalty Period and until the end of the Reduced Royalty Period, in lieu of the royalty rates set forth in TABLE 4 of Section 6.10.1, Biogen will pay Ionis royalty rates (the "***Biogen Reduced Royalty***") on Net Sales of Collaboration Products calculated on a Calendar Year-by-Calendar Year basis by [***]; *provided, however*, that the Biogen Reduced Royalty rate in each country will in no event exceed the [***].

(d) **End of Royalty Obligation for Collaboration Products**. On a country-by-country and Collaboration Product-by-Collaboration Product basis, other than [***], Biogen's obligation to make royalty payments hereunder for such Collaboration Product in such country will end on the expiration of the Reduced Royalty Period in such country. "***Reduced Royalty Period***" means, on a country by country basis, the period commencing upon the expiration of the [***] for such Collaboration Product in such country and ending when the [***].

(e) **Royalty Examples**. SCHEDULE 6.10.2(e) attached hereto contains examples of how royalties will be calculated under this Section 6.10.

(f) **Allocation of Net Sales**. If, by reason of one or more royalty rate adjustments under this Section 6.10.2, different royalty rates apply to Net Sales of Collaboration Products from different countries, Biogen will [***] such Net Sales [***]. SCHEDULE 6.10.2(f) attached hereto contains examples of how Net Sales of Collaboration Products from different countries at different royalty rates will be [***].

6.11. Limitation on Aggregate Reduction for Royalties for Collaboration Products.

6.11.1. In no event will the aggregate royalty reductions under Section 6.10.2(b) and Section 6.10.2(c) reduce the royalties payable to Ionis on Net Sales of a Collaboration Product in any given period to an amount that is less than the [***] for such Collaboration Product.

6.11.2. In no event will the aggregate royalty offsets under Section 6.13.3(b), Section 6.13.3(d) and Section 7.1.3(b) reduce the royalties payable to Ionis on Net Sales of a Collaboration Product in any given period to an amount that is less than the greater of [***].

For example, if the Royalty Quotient during a given Calendar Year in the Reduced Royalty Period is less than [***]%, then the offsets under Section 6.13.3(b), Section 6.13.3(d) and Section 7.1.3(b) will not apply during such Calendar Year but the full Royalty Quotient reduction pursuant to Section 6.10.2(c) will apply.

As an additional example, if the Royalty Quotient during a given Calendar Year in the Reduced Royalty Period is [***]%, and the [***] in such Calendar Year are [***]% of the applicable royalty rates in TABLE 4 of Section 6.10.1, then Biogen may apply the offsets under Section 6.13.3(b), Section 6.13.3(d) and Section 7.1.3(b) until the actual royalty payment made to Ionis in such Calendar Year is equal to [***]% of the applicable royalty rates in TABLE 4 of Section 6.10.1.

6.12. Reverse Royalty Payments to Biogen for a Discontinued Collaboration Product.

6.12.1. **Reverse Royalty for a Discontinued Collaboration Product**. If Ionis or any of its Affiliates or Sublicensees Commercializes a Discontinued Collaboration Product for which Biogen has paid Ionis the license fee under Section 6.5, then following the First Commercial Sale of such Discontinued Collaboration Product by Ionis or its Affiliates or Sublicensees, Ionis will pay Biogen or its designated Affiliate a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Collaboration Product ("***Reverse Royalties***"). Ionis' obligation to pay Biogen Reverse Royalties will [***].

6.12.2. **Applicable Royalty Provisions**. In addition to this Section 6.12, the definition of Net Sales in APPENDIX 1 and the other provisions contained in this ARTICLE 6 governing payment of royalties from Biogen to Ionis will govern the payment of Reverse Royalties from Ionis to Biogen under this Section 6.12, *mutatis mutandis*, including the provisions of Sections 6.10.2, 6.13, 6.14, 6.15, 6.16, and 6.17.

6.13. Third Party Payment Obligations.

6.13.1. Existing Ionis In-License Agreements.

(a) Certain of the Licensed Technology Controlled by Ionis as of the Effective Date licensed to Biogen under Section 4.1.1(a) or Section 4.1.1(b) were in-licensed or were acquired by Ionis under the agreements with Third Party licensors or sellers listed on SCHEDULE 6.13.1 or in a separate written agreement between the Parties (all such license or purchase agreements being the "***Ionis In-License Agreements***"), and certain milestone or royalty payments and license maintenance fees may become payable by Ionis to such Third Parties under the Ionis In-License Agreements based on the Development and Commercialization of a Product by Biogen under this Agreement.

(b) Any payment obligations arising under the Ionis In-License Agreements as existing on the Effective Date as they apply to Collaboration Products for High Interest Targets designated as of the Effective Date, will be paid by [***] as [***].

6.13.2. New In-Licensed Ionis Product-Specific Patents; Ionis Manufacturing and Analytical Patents. If after the Effective Date, Ionis obtains Third Party Patent Rights necessary or useful to Develop, Manufacture or Commercialize a Product that would have been considered an Ionis Product-Specific Patent had Ionis Controlled such Patent Rights on the Effective Date, to the extent Controlled by Ionis, Ionis will include such Third Party Patent Rights in the license granted to Biogen under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) if Biogen agrees in writing to pay Ionis as [***].

6.13.3. Additional Core IP In-License Agreements.

(a) Biogen will promptly provide Ionis written notice of any Additional Core IP Biogen believes it has identified and Ionis 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 Ionis obtains such a Third Party license, Ionis will include such Additional Core IP in the license granted to Biogen under Section 4.1.1(a), and any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

(b) If, however, Ionis elects not to obtain such a license to such Third Party intellectual property, Ionis will so notify Biogen, and Biogen may obtain such a Third Party license and, subject to Section 6.11.2, Biogen may offset an amount equal to [***]% of any [***] paid by Biogen 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 Biogen pursuant to Section 6.13.3(a) is Additional Core IP under Section 6.13.3(b), Ionis will send written notice to such effect to Biogen, and the Parties will engage a mutually agreed upon independent Third Party intellectual property lawyer with expertise in the patenting of oligonucleotides, 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 Biogen is permitted to [***]. The costs of any Third Party expert engaged under this Section 6.13.3(c) will be paid by the Party against whose position the Third Party lawyer's determination is made.

(d) Notwithstanding the determination of the Third Party lawyer under Section 6.13.3(c), if a Third Party Controlling Additional Core IP is awarded a judgment from a court of competent jurisdiction arising from its claim against Biogen asserting that [***], Biogen will be permitted to [***].

6.13.4. Other Third Party Payments.

(a) **Ionis' Third Party Agreements**. Except as otherwise expressly agreed to by Biogen under Section 6.13.2, after Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) for a particular Product, Biogen will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Ionis where either [***].

(b) **Biogen's Third Party Agreements**. Without limiting any applicable [***] under Section 6.13.3(b), Biogen will be responsible for paying [***]% of the [***] arising under any Third Party agreements entered into by Biogen as they apply to Products.

6.14. Payments.

6.14.1. Commencement. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, Biogen will make royalty payments to Ionis under this Agreement within [***] following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for Products during the relevant Calendar Quarter and the calculation of royalties due thereon, including country, units, sales price, the exchange rate used and the type of Product (i.e., whether it is a Collaboration Product or Biogen Alternate Modality Product) and the aggregate reduction to gross sales to arrive at Net Sales. Following the end of the first full Calendar Quarter subsequent to First Commercial Sale in a Major Market of any Product (but not in any subsequent Calendar Quarter unless there is a material change in the amount of any reduction to gross sales or the methodology used by Biogen to calculate any such reduction), Biogen will also include in such report a description of the reductions to gross sales to arrive at Net Sales, broken down by each category of reduction listed in clauses (a) through (d) of the definition of "Net Sales" and a non-binding qualitative analysis describing how Biogen anticipates such reductions may fluctuate over time. If no royalties are payable in respect of a given Calendar Quarter, Biogen will submit a written royalty report to Ionis so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, within [***] following the end of each such Calendar Quarter, Biogen will provide Ionis a [***] report estimating the total Net Sales of, and royalties payable to Ionis for Products projected for such Calendar Quarter.

6.14.2. **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 Ionis in writing, and (iii) non-creditable ([***]), irrevocable and non-refundable. Whenever for the purposes of calculating the royalties payable under this Agreement conversion from any foreign currency will be required, all amounts will first be calculated in the currency of sale and then converted into United States dollars by applying the monthly average rate of exchange calculated by using the foreign exchange rates published in Bloomberg during the applicable month starting two Business Days before the beginning of such month and ending two Business Days before the end of such month as utilized by Biogen, in accordance with generally accepted accounting principles, fairly applied and as employed on a consistent basis throughout Biogen's operations.

6.14.3. **Records Retention**. Commencing with the First Commercial Sale of a Product, Biogen will keep complete and accurate records pertaining to the sale of Products for a period of [***] after the year in which such sales occurred, and in sufficient detail to permit Ionis to confirm the accuracy of the Net Sales or royalties paid by Biogen hereunder.

6.14.4. **No Payments for non-ASOs for Pre-Existing Targets**. For the avoidance of doubt, in no event shall any payments be due to Ionis under this Agreement with respect to any non-oligonucleotide product developed or commercialized for a Pre-Existing Target.

6.15. **Audits**. After Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) for a particular Product, during the Agreement Term and for a period of [***] thereafter, at the request and expense of Ionis, Biogen will permit an independent certified public accountant of nationally recognized standing appointed by Ionis, at reasonable times and upon reasonable notice, but in no case more than [***], to examine such records as may be necessary for the purpose of verifying the calculation and reporting of Net Sales and the correctness of any royalty payment made under this Agreement for any period within the preceding [***]. As a condition to examining any records of Biogen, such auditor will sign a nondisclosure agreement reasonably acceptable to Biogen in form and substance. Any and all records of Biogen examined by such independent certified public accountant will be deemed Biogen's Confidential Information. Upon completion of the audit, the accounting firm will provide both Biogen and Ionis with a written report disclosing whether the royalty payments made by Biogen are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of Biogen, it is shown that Biogen's payments under this Agreement were less than the royalty amount which should have been paid, then Biogen will make all payments required to be made by paying Ionis 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 6.17. If, as a result of any inspection of the books and records of Biogen, it is shown that Biogen's payments under this Agreement were greater than the royalty amount which should have been paid, then [***]; *provided, however,* that if [***]. Ionis will pay for such audit, except that if Biogen is found to have underpaid Ionis by more than [***]% of the amount that should have been paid, Biogen will reimburse Ionis' reasonable costs of the audit.

6.16. Taxes.

6.16.1. 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.

6.16.2. Withholding Tax.

(a) The Parties agree to cooperate with one another and use reasonable efforts to lawfully avoid or reduce tax 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. To the extent the paying Party is required to deduct and withhold taxes, interest or penalties on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are entitled to do so.

(b) With respect to any commercial supply agreement entered between the Parties for the commercial supply of API under this Agreement, such supply agreement will (i) provide that only Biogen will claim any tax benefit allowed under IRC Section 199 Income Attributable to Domestic Production Activities, and (ii) include compensation to Ionis reflecting the value of the reasonably anticipated tax benefit under IRC Section 199 Income Attributable to Domestic Production Activities forfeited by Ionis. If the IRS determines that Biogen is not entitled to the tax benefits under Section 199, Ionis is not required to reimburse Biogen for this tax benefit unless Ionis receives a cash benefit on its federal tax return. A cash benefit will include any utilization of net operating losses that were generated in a year in which Ionis claimed any IRC Sec 199 deduction. The reimbursement to Biogen would be an amount equal to the Section 199 deduction times thirty-five percent, less any administrative costs to compute the tax benefit. The reimbursement would be due to Biogen within 90 days after filing any original or amended federal tax return. If the IRS determines that Ionis is not eligible for the tax benefit or determines the tax benefit should be a different amount, Biogen will pay back to Ionis the amount of any adjustment. Ionis will notify Biogen within 30 days of filing a return that claims such deduction or utilizes a related net operating loss.

6.16.3. **Tax Cooperation**. Ionis will provide Biogen with any and all tax forms that may be reasonably necessary in order for Biogen to lawfully not withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Following Biogen's timely receipt of such tax forms from Ionis, Biogen 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. Ionis will provide any such tax forms to Biogen upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to determine if any taxes are applicable to payments under this Agreement and 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 6.16.

The provisions of this Section 6.16 are to be read in conjunction with the provisions of Section 12.4 below.

6.17. **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.

ARTICLE 7.
INTELLECTUAL PROPERTY

7.1. **Ownership**.

7.1.1. **Ionis Technology and Biogen Technology**. As between the Parties, Ionis will own and retain all of its rights, title and interest in and to the Licensed Know-How and Licensed Patents and Biogen will own and retain all of its rights, title and interest in and to the Biogen Know-How and Biogen 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, Biogen is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Biogen or its Affiliates under this Agreement ("***Biogen Program Know-How***") and any Patent Rights that claim or cover Biogen Program Know-How ("***Biogen Program Patents***" and together with the Biogen Program Know-How, the "***Biogen Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by Biogen to Ionis under this Agreement. As between the Parties, Ionis is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Ionis or its Affiliates ("***Ionis Program Know-How***") and any Patent Rights that claim or cover such Know-How ("***Ionis Program Patents***" and together with the Ionis Program Know-How, the "***Ionis Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any assignment, rights or licenses expressly granted by Ionis to Biogen under this Agreement. Any Know-How discovered, developed, invented or created jointly under this Agreement 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 Biogen and Ionis 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 Biogen Program Patents, Ionis 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 ARTICLE 7. Ionis' obligation to participate in the JPC will terminate upon Biogen's exercise of (or the expiration or termination of) the last Option. Thereafter, Ionis will have the right, but not the obligation, to participate in JPC meetings. A strategy will be discussed with regard to intellectual property considerations when selecting each Development Candidate, prosecution and maintenance, defense and enforcement of Ionis Product-Specific Patents that would be or are licensed to Biogen under Section 4.1.1 in connection with a Product and Biogen Product-Specific Patents, defense against allegations of infringement of Third Party Patent Rights, and licenses to Third Party Patent Rights or Know-How, 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 designate a Development Candidate or prosecute, enforce and defend such Patent Rights, as applicable, hereunder, but will not be binding on such Party.

(b) Ionis or Biogen (as applicable) will provide the Joint Patent Committee with notice of any Know-How or Patent Rights discovered, developed, invented or created jointly by such Party and a Third Party in the performance of activities under the Neurology Plans or solely by a Third Party performing activities under the Neurology Plans on such Party's behalf (such Know-How and Patent Rights, the "***Collaborator IP***") promptly after such Party receives notice or otherwise becomes aware of the existence of such Collaborator IP. The JPC will determine whether any such Collaborator IP would be infringed by the Development, registration, Manufacture or Commercialization of the applicable Development Candidate or any Compound under consideration by Ionis for potential designation as a Development Candidate. If the JPC (or independent patent counsel engaged pursuant to this Section 7.1.3(b)) determines that any Collaborator IP would be infringed by such Development, registration, Manufacture or Commercialization, [***]; *provided that*, if such Party is unable to obtain [***] license to such Collaborator IP or if the Parties mutually agree that it is not necessary to obtain [***] license, such Party shall use Commercially Reasonable Efforts to obtain a [***] license to such Collaborator IP from such Third Party (any such [***] with such Third Party, a "***Collaborator License***"), and in each case such Party will endeavor to obtain in such Collaborator License the right to sublicense such Collaborator IP to the other Party on terms that contain no greater restrictions on the other Party's use of such Collaborator IP than those set forth in this Agreement.

Notwithstanding any provision to the contrary in this Agreement, except for [***] obligation to pay any costs arising under any Third Party agreement as a result of granting Biogen the license under Section 4.4.1(b), if Collaborator IP (other than Additional Core IP) arises from activities performed by a Third Party under the applicable Neurology Plan, then any payment obligations arising under the applicable Collaborator License based on the Development or Commercialization of a Product will be paid as follows: (A) in the case where [***] enters into such Collaborator License, [***] will be solely responsible for paying any payment obligations that [***], and [***] will be solely responsible for paying any payment obligations that [***], and (B) in the case where [***] enters into such Collaborator License, [***] will be [***] responsible for paying any payment obligations that [***].

With respect to any such Collaborator IP licensed by Ionis under a Collaborator License with such Third Party, Biogen will have the right in accordance with Section 4.1.5 to elect to exclude any such Collaborator IP from the applicable license granted to Biogen under Section 4.1.1 by providing Ionis written notice prior to Option exercise. If, prior to the date the applicable license under Section 4.1.1 is granted hereunder, Biogen provides Ionis with such a written notice to exclude certain of such Collaborator IP from such license, such Collaborator IP will not be included in the Licensed Technology licensed with respect to the applicable Products under this Agreement. If Biogen does not provide Ionis with such a written notice to exclude such Collaborator IP prior to the date the applicable license under Section 4.1.1 is granted hereunder, such Collaborator IP (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.

In case of a dispute in the Joint Patent Committee over whether any Collaborator IP would be infringed by the Development, registration, Manufacture or Commercialization of the applicable Development Candidate or any Compound under consideration by Ionis for potential designation as the Development Candidate, at the non-contracting Party's request, 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, taking into account any existing prior art. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be borne by the non-contracting Party.

(c) 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 Ionis and Biogen) over inventorship of Program Patents, if the Joint Patent Committee cannot resolve such dispute, even after seeking the CSC'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.

(d) 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 ARTICLE 7. The JPC will determine by unanimous consent 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.

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. On a Collaboration Program-by-Collaboration Program basis or Biogen Alternate Modality Target-by-Biogen Alternate Modality Target basis (as applicable), until the earlier of the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) and the expiration or termination of Biogen's right to be granted such license, Ionis will use Commercially Reasonable Efforts to diligently Prosecute and Maintain all Ionis Product-Specific Patents and any Jointly-Owned Program Patents Covering Products, in each case to the extent that Ionis has the right to Prosecute and Maintain such Patent Rights.

7.2.2. Licensed Patents and Biogen Patents.

(a) Licensed Patents In General. Prior to the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of all Licensed Patents that are the subject of such license grant, subject to Section 7.2.2(b) and Section 7.2.3. During the Agreement Term, Ionis will control and be responsible for all aspects of the Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents.

(b) Licensed Patents After License Grant. After Ionis assigns to Biogen or one or more designated Affiliates Ionis' ownership interest in (i) all Ionis Product-Specific Patents that are owned (whether solely owned or jointly owned with one or more Third Parties) by Ionis, and (ii) any Jointly-Owned Program Patents Covering Products in accordance with Section 4.2, Biogen will control and be responsible for all aspects of the Prosecution and Maintenance of all such Ionis Product-Specific Patents and Jointly-Owned Program Patents to the same extent Ionis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such assignment, subject to Section 7.2.3, and will grant Ionis the license set forth in Section 4.2.2.

(c) **Biogen Patents**. Biogen will control and be responsible for all aspects of the Prosecution and Maintenance of all Biogen Patents, subject to Section 7.2.3.

7.2.3. **Jointly-Owned Program Patents**. Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that do not Cover Products. Prior to the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents Covering Products that are the subject of such license. After the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), Biogen will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents Covering Products that are the subject of such license.

7.2.4. **Prosecution of Multi-Indication Product-Specific Patents; Biogen Supremacy to Enforce and Extend**. With respect to Product-Specific Patent Rights related to Multi-Indication Products, the Parties will endeavor to prosecute such Patent Rights to claim inventions related to Neurological Diseases separately from inventions related to Non-Neurological Indications. If there is an Ionis Product-Specific Patent that Covers both (i) a Multi-Indication Product licensed to Biogen under Section 4.1.1(a), and (ii) a Multi-Indication Product of Ionis (each such Ionis Product-Specific Patent, a "***Multi-Indication Product-Specific Patent***"), then so long as Biogen is Developing and Commercializing such Multi-Indication Product pursuant to its license under Section 4.1.1(a), Biogen will have the sole and exclusive right, but not the obligation, to institute and control any (i) Proceeding related to the infringement of such Multi-Indication Product-Specific Patent, (ii) Prosecution and Maintenance of such Multi-Indication Product-Specific Patent and (iii) patent term extension related to such Multi-Indication Product-Specific Patent.

7.2.5. **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 Ionis Core Technology Patents set forth on SCHEDULE 8.2.4(a), together with all 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 7.2.5, 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 Biogen elects (a) not to file and prosecute patent applications for the Jointly-Owned Program Patent Rights or Ionis Product-Specific Patents that have been licensed or assigned to Biogen under this Agreement or the Biogen Product-Specific Patents ("***Biogen-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 Biogen-Prosecuted Patent in a particular country, or (c) not to file and prosecute patent applications for the Biogen-Prosecuted Patent in a particular country following a written request from Ionis to file and prosecute in such country, then Biogen will so notify Ionis promptly in writing of its intention (including a reasonably detailed rationale for doing so) in good time to enable Ionis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and except as set forth in Section 7.2.5(c) Ionis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such Biogen-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, Biogen will cooperate with Ionis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such Biogen-Prosecuted Patent in such country in Ionis' own name, but only to the extent that Biogen is not required to take any position with respect to such abandoned Biogen-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 Biogen under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Ionis assumes responsibility for the Prosecution and Maintenance of any such Biogen-Prosecuted Patent under this Section 7.2.5(b), Ionis will have no obligation to notify Biogen if Ionis intends to abandon such Biogen-Prosecuted Patent.

(c) Notwithstanding Section 7.2.5(b) above, if, after having consulted with outside counsel, Biogen reasonably determines that filing or continuing to prosecute a patent application in a particular country for a Biogen-Prosecuted Patent (the "***Conflicting Patent Right***") is reasonably likely to adversely affect the scope, validity or enforceability of a patent application or issued patent in a particular country for another Biogen-Prosecuted Patent (the "***Superior Patent Right***"), in each case where both the Conflicting Patent Right and the Superior Patent Right if issued would meet the criteria set forth in clause (i) of Section 6.10.2(a), then *so long as* Biogen continues to Prosecute and Maintain the Superior Patent Right in accordance with this Agreement, Ionis will not have the right under Section 7.2.5(b) above to file or prosecute the Conflicting Patent Right.

(d) If, during the Agreement Term, Ionis intends to abandon any Ionis Product-Specific Patent for which Ionis is responsible for Prosecution and Maintenance without first filing a continuation or substitution, then, if Biogen's right to obtain a license under Section 4.1.1 to such Ionis Product-Specific Patent has not expired or terminated, Ionis will notify Biogen of such intention at least [***] days before such Patent Right will become abandoned, and Biogen 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 Biogen assumes responsibility for the Prosecution and Maintenance of any such Ionis Product-Specific Patent under this Section 7.2.5(d), Biogen will have no obligation to notify Ionis if Biogen intends to abandon such Ionis Product-Specific Patent.

(e) 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.

(f) 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 [***] 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 7.2.5(f), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Program Patents.

(g) 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, Ionis and Biogen 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 Biogen Patents**. Except as set forth in 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 the date the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) is granted to Biogen, Biogen will be solely responsible for Patent Costs arising from the Prosecution and Maintenance of the Ionis 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) Ionis will have the first right, but not the obligation, to defend against any such Proceeding initiated prior to the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) at its sole cost and expense, and (b) Biogen will have the first right, but not the obligation, to defend against any such Proceeding initiated after the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) 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 [***] 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 Collaboration 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 Collaboration Product, Ionis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. Biogen will reasonably assist Ionis in defending such Proceeding and cooperate in any such litigation at the request and expense of Ionis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Ionis will provide Biogen with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Ionis becomes aware and that is of the type described in this Section 7.4.2, and Ionis will promptly furnish Biogen with a copy of each communication relating to the alleged infringement received by Ionis.

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 (e.g., a counterclaim of infringement), 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 (i) a product directed against the RNA that encodes a Collaboration Target in the Field, or (ii) a non-oligonucleotide product that is designed to bind, mimic or otherwise affect a protein or RNA that is encoded by a Biogen Alternate Modality Target ("***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 License Grant**. For any Competitive Infringement with respect to a Product occurring after the Effective Date but before the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), Ionis 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 Biogen will have the right to be represented in that action by counsel of its own choice at its own expense, *however*, Ionis will have the sole right to control such litigation. Ionis will provide Biogen with prompt written notice of the commencement of any such Proceeding, and Ionis will keep Biogen apprised of the progress of such Proceeding. If Ionis 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 Ionis has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Biogen will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice; *provided* that Ionis will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Ionis 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 Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents.

7.5.3. **Following License Grant**. For any Competitive Infringement with respect to a particular Product (except for a Discontinued Collaboration Product) occurring after the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), so long as part of such Proceeding Biogen also enforces any Patent Rights Controlled by Biogen (including any Ionis Product-Specific Patents assigned by Ionis to Biogen under this Agreement) being infringed that Cover the Product, then Biogen 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 at its own expense, and Ionis will have the right, at its own expense, to be represented in that action by counsel of its own choice, *however,* Biogen will have the right to control such litigation. If Biogen 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 Biogen has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Ionis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and Biogen will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Ionis 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 Ionis Core Technology Patents or Ionis Manufacturing and Analytical 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 the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) will be (i) [***]; or (ii) [***]; then

(c) any remaining proceeds constituting direct or actual damages for acts of infringement occurring after the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) [***]; 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 ARTICLE 6, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 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 Biogen 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, [***]; 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 Ionis**. Ionis will retain all rights to pursue an infringement of any Patent Right solely owned by Ionis which is other than a Competitive Infringement and Ionis will retain all recoveries with respect thereto.

7.6.3. **Patents Solely Owned by Biogen**. Biogen will retain all rights to pursue an infringement of any Patent Right solely owned by Biogen which is other than a Competitive Infringement and Biogen will retain all recoveries with respect thereto.

7.7. Patent Listing.

7.7.1. **Biogen's Obligations**. Biogen 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 Biogen 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, Biogen will retain final decision-making authority as to the listing of all applicable Patent Rights for the Product that are not Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents, regardless of which Party owns such Patent Rights.

7.7.2. **Ionis' Obligations**. Ionis will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Discontinued Collaboration Product. Prior to such listings, the Parties will meet, through the Joint Patent Committee, to evaluate and identify all applicable Patent Rights, and Ionis 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, Ionis will retain final decision-making authority as to the listing of all applicable Patent Rights for such Discontinued Collaboration Products, as applicable, regardless of which Party owns such Patent Rights.

7.8. **Joint Research Agreement under the Leahy-Smith America Invents Act**. Notwithstanding anything to the contrary in this ARTICLE 6, neither Party will have the right to make an election under 35 U.S.C. § 102(c) of the Leahy-Smith America Invents Act when exercising its rights under this ARTICLE 6 without the prior written consent of the other Party, which will not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, each Party will use reasonable efforts to cooperate and coordinate their activities with the other 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 ARTICLE 6 will be subject to the Third Party rights and obligations under any (i) New Third Party License the restrictions and obligations of which Biogen has agreed to under Section 6.13.2, (ii) Prior Agreements, and (iii) Ionis In-License Agreements; *provided*, *however*, that, to the extent that Ionis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to Biogen hereunder and, this Agreement purports to grant any such rights to Biogen, Ionis will act in such regard with respect to such Patent Rights at Biogen's direction.

7.10. **Additional Right and Exceptions**. Notwithstanding any provision of this ARTICLE 6, Ionis retains the sole right to Prosecute and Maintain Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents during the Agreement Term and to control any enforcement of Ionis Core Technology Patents and Ionis 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 Ionis and Covering the Ionis Core Technology Patents or Ionis 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 the date Biogen is granted the license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable), Biogen will determine which relevant patents will be extended.

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 Collaboration Program.

8.2. **Representations and Warranties of Ionis**. Ionis hereby represents and warrants to Biogen, 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 Biogen under Section 4.1.1(a) upon the exercise of the Option for a Collaboration Product arising under the Collaboration Programs) under any intellectual property owned or Controlled by Ionis or its Affiliates as of the Effective Date that would be required in order for Biogen to further Develop and Commercialize a Collaboration Product.

8.2.2. The Licensed Technology existing as of the Effective Date constitutes all of the Patent Rights and Know-How Controlled by Ionis as of the Effective Date that are necessary to Develop, Manufacture or Commercialize Compounds contemplated under the Collaboration Programs in the Field. Ionis has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in the Licensed Technology in a manner that conflicts with any rights granted to Biogen hereunder with respect to Collaboration Products.

8.2.3. Neither Ionis nor its Affiliates owns or Controls any Patent Rights or Know-How covering formulation or delivery technology as of the Effective Date that would be useful or necessary in order for Biogen to further Develop or Commercialize Compounds contemplated under the Collaboration Programs.

8.2.4. SCHEDULE 8.2.4(a) and SCHEDULE 8.2.4(b) set forth true, correct and complete lists of all Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents that apply to the Compounds contemplated under the Collaboration Programs as of the Effective Date (the "***Ionis Platform Technology***"), respectively, and indicates whether each such Patent Right is owned by Ionis or licensed by Ionis from a Third Party and if so, identifies the licensor or sublicensor from which the Patent Right is licensed. Ionis 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 Biogen under this Agreement.

8.2.5. There are no claims, judgments or settlements against or owed by Ionis or its Affiliates or pending against Ionis or, to the best of Ionis' knowledge, threatened against Ionis, in each case relating to the Ionis Platform Technology, Ionis Manufacturing and Analytical Know-How, Ionis Know-How, Collaboration Targets or High Interest Targets that could impact activities under this Agreement. To the best of Ionis' 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 Ionis Platform Technology, Ionis Manufacturing and Analytical Know-How, Ionis Know-How or High Interest Targets that would impact activities under this Agreement.

8.2.6. At the Effective Date (a) there is no fact or circumstance known by Ionis that would cause Ionis to reasonably conclude that any Ionis Core Technology Patent or Ionis Manufacturing and Analytical Patent is invalid or un-enforceable, (b) there is no fact or circumstance known by Ionis that would cause Ionis to reasonably conclude the inventorship of each Ionis Core Technology Patent or Ionis Manufacturing and Analytical Patent is not properly identified on each patent, and (c) all official fees, maintenance fees and annuities for the Ionis Core Technology Patent or Ionis Manufacturing and Analytical Patent have been paid and all administrative procedures with governmental agencies have been completed.

8.2.7. Ionis has set forth on SCHEDULE 6.13.1 or in a separate written agreement with Biogen true, correct and complete lists of the agreements with Third Party licensors or sellers pursuant to which Ionis has licensed or acquired the Licensed Technology Controlled by Ionis as of the Effective Date licensed to Biogen under Section 4.1.1(a) that is necessary or useful to conduct the research, Development, Manufacture or Commercialization of any High Interest Target listed on the High Interest Target List as of the Effective Date. All Ionis In-License Agreements are in full force and effect and have not been modified or amended. Neither Ionis nor, to the best knowledge of Ionis, the Third Party licensor in an Ionis In-License Agreement is in default with respect to a material obligation under such Ionis 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 Ionis In-License Agreement.

8.2.8. SCHEDULE 8.2.8 is a complete and accurate list of all agreements that create Third Party Obligations with respect to the Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents that affect the rights granted by Ionis to Biogen under this Agreement with respect to Collaboration Programs.

8.3. **Ionis Covenants**. Ionis hereby covenants to Biogen that, except as expressly permitted under this Agreement:

8.3.1. Ionis will promptly amend SCHEDULE 8.2.4(a), SCHEDULE 8.2.4(b) and SCHEDULE 8.2.4(c) and submit such amended Schedules to Biogen if Ionis becomes aware that any Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents or Ionis Product-Specific Patents are not properly identified on such Schedule.

8.3.2. during the Agreement Term, Ionis will maintain and not breach any Ionis 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 Ionis that are Controlled by Ionis and are licensed or may become subject to a license from Ionis to Biogen for a Development Candidate under this Agreement;

8.3.3. Ionis will promptly notify Biogen of any material breach by Ionis or a Third Party of any New Third Party License, and in the event of a breach by Ionis, will permit Biogen to cure such breach on Ionis' behalf upon Biogen's request;

8.3.4. Ionis will not amend, modify or terminate any Ionis In-License Agreement or New Third Party License in a manner that would adversely affect Biogen's rights hereunder without first obtaining Biogen's written consent, which consent may be withheld in Biogen's sole discretion;

8.3.5. Ionis will not enter into any new agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case that restricts, limits or encumbers the rights granted to Biogen under this Agreement;

8.3.6. Ionis will cause its Affiliates, licensees and sublicensees to comply with the terms of Section 2.1;

8.3.7. all employees and contractors of Ionis performing Development activities hereunder on behalf of Ionis will be obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to Ionis or such Affiliate, respectively, as the sole owner thereof; and

8.3.8. If, after the Effective Date, Ionis becomes the owner or otherwise acquires Control of any formulation or delivery technology that would be necessary or useful in order for Biogen to further Develop, Manufacture or Commercialize a Collaboration Product, and Biogen has exercised its Option and the license granted to Biogen under this Agreement is in effect, Ionis will make such technology available to Biogen on commercially reasonable terms.

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. BIOGEN AND IONIS 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 Biogen**. Biogen will indemnify, defend and hold harmless Ionis 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 Biogen, its Affiliates or Sublicensees and its or their respective directors, officers, employees and agents, in connection with Biogen'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 Biogen 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 Biogen or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Ionis pursuant to this Agreement); or

9.1.4. the Commercialization of a Product by or on behalf of Biogen 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 Ionis or its Affiliates, licensees, Sublicensees or contractors, and it's or their respective directors, officers, employees and agents or other circumstance for which Ionis has an indemnity obligation pursuant to Section 9.2.

9.2. **Indemnification by Ionis**. Ionis will indemnify, defend and hold harmless Biogen 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 Ionis, its Affiliates or Sublicensees or its or their respective directors, officers, employees and agents, in connection with Ionis' 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 Ionis under ARTICLE 8 or any other provision under this Agreement;

9.2.3. any Development or Manufacturing activities that are conducted by or on behalf of Ionis or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Biogen pursuant to this Agreement); or

9.2.4. any development, manufacturing or commercialization activities that are conducted by or on behalf of Ionis or its Affiliates or Sublicensees with respect to a Discontinued Collaboration 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 Biogen or its Affiliates, licensees, Sublicensees or contractors and its or their respective directors, officers, employees and agents or other circumstance for which Biogen 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. Ionis' Insurance Obligations. Ionis 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, Ionis will maintain, in force from [***] days prior to enrollment of the first patient in a Clinical Study, a [***] insurance policy providing coverage of at least $[***] per claim and $[***] Annual aggregate. Ionis will furnish to Biogen evidence of such insurance upon request.

9.4.2. Biogen's Insurance Obligations. Biogen 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, Biogen will maintain, in force from [***] days prior to enrollment of the first patient in a Clinical Study, a [***] 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 Biogen initiates the First Commercial Sale of a Product hereunder. Biogen will furnish to Ionis evidence of such insurance upon request. Notwithstanding the foregoing, Biogen 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 Biogen'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 OF THIS AGREEMENT, (c) A PARTY'S BREACH OF ARTICLE 2, OR A BREACH OF SECTION 10.4.4(a) BY BIOGEN 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 this Agreement expires as follows:

10.1.1. on a country-by-country basis, on the date of expiration of all payment obligations by the Commercializing Party under this Agreement with respect to all Products (or Discontinued Collaboration Product(s)) in such country;

10.1.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to all Products (or Discontinued Collaboration Products) in all countries pursuant to Section 10.1.1;

10.1.3. where there are no Collaboration Targets and no Biogen Alternate Modality Targets designated by the expiration of the Research Term as described in Section 1.9;

10.1.4. where there are no Biogen Alternate Modality Targets designated by the expiration of the Research Term as described in Section 1.9, and no Development Candidates designated by the expiration of the ASO Development Candidate Identification Term as described in Section 1.10.1(d); and

10.1.5. where there are no Biogen Alternate Modality Targets designated by the expiration of the Research Term as described in Section 1.9, and every Option has expired as a result of Biogen not providing Ionis a written notice stating Biogen is exercising such Options and paying Ionis the applicable license fees under Section 6.6 by the Option Deadline, or as a result of Section 1.10.2(g) or Section 10.4.3.

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. **Biogen's Termination for Convenience**. At any time following payment by Biogen of the upfront fee under Section 6.1, subject to Section 10.4.1 below, Biogen will be entitled to terminate this Agreement as a whole, or terminate this Agreement in part with respect to a particular Collaboration Program or Biogen Alternate Modality Target, for convenience by providing 90 days written notice to Ionis of such termination.

10.2.2. **Termination for Failure to Divest Directly Competitive Collaboration Product**. If a Competing Collaboration Acquirer or Competing Alternate Modality Acquirer, as applicable, does not, during the Collaboration Divestiture Period or Alternate Modality Divestiture Period, as applicable, divest itself of a Directly Competitive Collaboration Product, Directly Competitive Collaboration Program, Directly Competitive Biogen Alternate Modality Product or Directly Competitive Biogen Alternate Modality Program, as applicable, or terminate the development and commercialization of such Directly Competitive Collaboration Product or Directly Competitive Biogen Alternate Modality Product or activities under such Directly Competitive Collaboration Program or Directly Competitive Biogen Alternate Modality Program, as applicable, or assign this Agreement to a Third Party that is not itself developing or commercializing such a Directly Competitive Biogen Alternate Modality Product, or engaged in such Directly Competitive Collaboration Program or Directly Competitive Biogen Alternate Modality Program, as applicable, as set forth in Sections 12.5.2 and 12.5.3, Biogen may terminate this Agreement solely with respect to the Collaboration Program or Biogen Alternate Modality Program affected thereby immediately upon providing written notice to Ionis.

10.2.3. Termination Due to Failure to Obtain HSR Clearance.

(a) If the Parties make an HSR Filing with respect to a proposed Biogen Alternate Modality Program or Collaboration Program under Section 1.7, Section 3.1.3 or Section 3.2.5 of this Agreement and the HSR Clearance Date has not occurred on or prior to 90 days after the effective date of the latest HSR Filing made by the Parties, this Agreement will terminate solely with respect to the applicable proposed Biogen Alternate Modality Program or Collaboration Program (i) at the election of either Party immediately upon notice to the other Party, if the FTC or the DOJ has instituted (or threatened to institute) any action, suit or proceeding including seeking, threatening to seek or obtaining a preliminary injunction under the HSR Act against Biogen and Ionis to enjoin or otherwise prohibit the transactions contemplated by this Agreement related to such proposed Biogen Alternate Modality Program or Collaboration Program, or (ii) at the election of either Party, immediately upon notice to the other Party, if the Parties have not resolved any and all objections of the FTC and DOJ as contemplated by Section 3.1.4(b). Notwithstanding the foregoing, this Section 10.2.3 will not apply if an HSR Filing is not required to fully perform this Agreement with respect to a proposed Biogen Alternate Modality Program or Collaboration Program, as applicable.

(b) If this Agreement is terminated with respect to a Collaboration Program in accordance with Section 10.2.3(a), then, *until* [***] as follows:

(i) If Ionis [***]; and

(ii) If Ionis, its Affiliates or the licensee [***].

Nothing in this Section 10.2.3(b) obligates Ionis to (y) [***] or (z) [***].

10.2.4. Termination for Material Breach.

(a) **Biogen's Right to Terminate**. If Biogen believes that Ionis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1, which is governed by Section 10.2.5 below), then Biogen may deliver notice of such material breach to Ionis. If the breach is curable, Ionis will have [***] days to cure such breach. If Ionis fails to cure such breach within the [***] day period, or if the breach is not subject to cure, Biogen may terminate this Agreement with respect to the Neurology Target or Collaboration Program affected by such breach by providing written notice to Ionis. 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 Neurology Target or Collaboration Program affected by such breach.

(b) **Ionis' Right to Terminate**. If Ionis believes that Biogen is in material breach of (i) a payment obligation under ARTICLE 6 or (ii) one or more material provisions of this Agreement where such material breaches have occurred multiple times over the course of at least a [***]-month period (where such material breach is not a single continuous event) demonstrating a pattern of failing to timely comply with Biogen's obligations under this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 5.1, which is governed by Section 10.2.5 below), then Ionis may deliver notice of such material breach to Biogen. If the breach is curable, Biogen will have [***] 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 [***] days following such notice). If Biogen fails to cure such breach within the [***] day or [***] day period, as applicable, or if the breach is not subject to cure, Ionis in its sole discretion may terminate this Agreement with respect to the Neurology Target or Collaboration Program affected by such breach by providing written notice thereof to Biogen.

10.2.5. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Ionis, in Biogen's reasonable determination, fails to use Commercially Reasonable Efforts in the activities contemplated in ARTICLE 1 prior to the date Biogen is granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) with respect to a particular High Interest Target or Collaboration Program, Biogen will notify Ionis and, within [***] days thereafter, Ionis and Biogen 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 Ionis' use of Commercially Reasonable Efforts in ARTICLE 1. Following such a meeting, if Ionis fails to use Commercially Reasonable Efforts as contemplated by ARTICLE 1 with respect to such High Interest Target or Collaboration Program, then subject to Section 10.2.6 below, Biogen will have the right, at its sole discretion, to (i) terminate this Agreement as it relates to the applicable High Interest Target or Collaboration Program or, (ii) if the breach involves a Collaboration Program prior to Option exercise, Biogen may elect to trigger the alternative remedy provisions of Section 10.3 below as it relates to the applicable Collaboration Program in lieu of terminating this Agreement for such Collaboration Program by providing written notice to Ionis. This Section 10.2.5(a) sets forth Biogen's sole and exclusive remedies if Ionis fails to use Commercially Reasonable Efforts in the activities contemplated in ARTICLE 1 prior to the date Biogen is granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable).

(b) If Biogen, in Ionis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 5.1 with respect to a Collaboration Program, Ionis will notify Biogen and, within [***] days thereafter, Ionis and Biogen 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 Biogen's use of Commercially Reasonable Efforts in Section 5.1. Following such a meeting, if Biogen fails to use Commercially Reasonable Efforts with respect to the applicable Collaboration Program as contemplated by Section 5.1, then subject to Section 10.2.6 below, Ionis will have the right, at its sole discretion, to terminate this Agreement as it relates to such Collaboration Program.

10.2.6. **Disputes Regarding Material Breach**. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.4 or Section 10.2.5 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 [***] day period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.2.4 or Section 10.2.5, or the alternative remedy provisions of Section 10.2.5, 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 [***] 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.

10.2.7. **Termination for Insolvency**.

(a) 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.

(b) 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.

10.2.8. **Termination for Patent Challenge**. Ionis may terminate this Agreement if Biogen (i) commences or otherwise voluntarily determines to participate in any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Licensed Patents, or (ii) directs, supports or actively assists any other Person in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such Licensed Patents and, in each case ((i) or (ii)), within [***] days' written notice from Ionis, Biogen fails to rescind any and all of such actions, *provided however* that, nothing in this clause prevents Biogen from taking any of the actions referred to in this clause and *provided further* that Ionis will not have the right to terminate if Biogen:

(a) takes any such action as described in clause (i) or (ii) above as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order, including asserting invalidity as a defense in any court proceeding brought by Ionis asserting infringement of a Licensed Patent; or

(b) Acquires a Third Party that has an existing challenge, whether in a court or administrative proceeding, against a Licensed Patent; or

(c) licenses a product for which Ionis has an existing challenge, whether in a court or administrative proceeding, against a Licensed Patent.

10.3. **Alternative Remedies to Termination Available to Biogen Prior to Option Exercise**. If, prior to Option exercise, with respect to a particular Collaboration Program Biogen elects to (i) exercise the alternative remedy provisions of this Section 10.3 in lieu of terminating this Agreement for such Collaboration Program by providing written notice of such election to Ionis in accordance with Section 10.2.5(a), or (ii) exercise the Option in accordance with [***], then, in each case, solely with respect to the Collaboration Program giving rise to Biogen's exercise of these alternative remedy provisions, this Agreement will continue in full force and effect with the following modifications:

(a) Ionis will have no further rights or obligations to Develop the Collaboration Product under the applicable Collaboration Program or participate in the Neurology JRC, the applicable Neurology JDC, JPC or any other subcommittees or working groups established pursuant to this Agreement. Biogen will solely make all decisions that this Agreement would otherwise require or permit the Neurology JRC, the applicable Neurology JDC, JPC or any other subcommittees or working groups, or the Parties collectively, to make; *provided*, *however*, that Biogen will not have the right to create any obligations or incur any liabilities for or on behalf of Ionis;

(b) effective as of the date of Biogen's notice to Ionis electing the alternative remedy provisions of this Section 10.3, Biogen will be deemed for all purposes of this Agreement to have exercised the applicable Option;

(c) Biogen will have and Ionis grants, the exclusive license granted to Biogen under Section 4.1.1(a) for the applicable Collaboration Program;

(d) Biogen may exclude Ionis from all discussions with Regulatory Authorities regarding the applicable Collaboration Products, except to the extent Ionis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law;

(e) Biogen's obligation to make further disclosures of Know-How or other information to Ionis regarding the applicable Collaboration Products pursuant to this Agreement (including pursuant to Section 4.9 and Section 5.2.7) will terminate, other than reports required by Section 6.14.1, Section 10.4.4 (if applicable), and as reasonably required to permit Ionis to perform its obligations under this Agreement; *provided* such remedy will not limit or diminish the scope of any licenses granted by Biogen to Ionis under this Agreement;

(f) Ionis will perform its obligations under Section 4.9 with respect to the applicable Collaboration Product within [***] days of Biogen electing to exercise its alternative remedies under this Section 10.3 or exercising the Option in accordance with [***], and will provide to Biogen and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Biogen in assuming complete responsibility for the Development and Manufacture of the applicable Collaboration Products in an efficient and orderly manner; and

(g) If such Collaboration Program is not an ALS Collaboration Program the financial provisions of ARTICLE 6 as they apply to such Collaboration Program will be modified as follows:

(i) *[***] Payments*. Biogen will [***]; and

(ii) *License Fee*. The license fee set forth in Section 6.6 for the applicable Collaboration Product will be [***]. Such [***] will be due within 90 days after [***] and Biogen's [***].

The milestone provisions of Section 6.7 and the royalty provisions of Section 6.10 will [***].

10.4. Consequences of Expiration or Termination of the Agreement.

10.4.1. 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 Biogen Alternate Modality Product or Collaboration Product (as applicable) 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 for a surviving Product. 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 1.9 (End of Research Term), Section 1.10.1(d) (End of ASO Development Candidate Identification Term), Section 2.1.1(f) (Failure to Defer or Designate a High Interest Target a Collaboration Target or Biogen Alternate Modality Target), Section 3.1.3 (Option and Option Deadline) (but only with respect to Biogen's transfer obligations thereunder), Section 4.1.3 (Effect of Termination on Sublicenses), Section 4.2.2 (Grant Back to Ionis), Section 4.3 (Data Licenses), Section 4.4.3 (Enabling License to Biogen), Section 4.4.4 (Enabling License to Ionis), Section 4.5 (Licenses to Ionis for Biogen Results), Section 4.6 (Right to Obtain Direct License from Biogen to Ionis Partner; Sublicensees of Ionis), Section 4.9.2 (Technology Transfer after Option Exercise) (but only to the extent necessary to satisfy the requirements of Section 10.4.4), Section 6.12 (Reverse Royalty Payments to Biogen for a Discontinued Collaboration Product), Section 6.14.3 (Records Retention), Section 6.15 (Audits), Section 7.1.1 (Ionis Technology and Biogen Technology), Section 7.1.2 (Agreement Technology), Section 8.4 (Disclaimer), ARTICLE 9 (Indemnification; Insurance), Section 10.2.3(b), Section 10.2.7 (Termination for Insolvency), Section 10.4 (Consequences of Expiration or Termination of the Agreement) (except Section 10.4.5 (Remedies Available to Biogen for Ionis' Material Breach After Option Exercise)), ARTICLE 11 (Confidentiality), ARTICLE 12 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

10.4.2. **Natural Expiration**. If this Agreement expires in accordance with Section 10.1.1 or Section 10.1.2, the following terms will apply to any Biogen Alternate Modality Product or Collaboration Product (as applicable) that is the subject of such expiration:

(a) **Perpetual, Royalty-Free Non-Exclusive License**. If Biogen has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) for a particular Product, then upon expiration of the Biogen Alternate Modality Royalty Period or Reduced Royalty Period, as the case may be, in all countries in which the applicable Products are being or have been sold, Ionis will and hereby does grant to Biogen a perpetual, non-exclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Ionis Know-How to Manufacture, Develop and Commercialize the applicable Product.

10.4.3. **Termination Before License Grant**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 before Biogen has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) for a particular Product, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to each Product, Neurology Target, High Interest Target or Collaboration Program that is the subject of such expiration or termination:

(a) Biogen's right to designate High Interest Targets as Collaboration Targets or Biogen Alternate Modality Targets under this Agreement will expire and Ionis will be free to Develop and Commercialize the applicable Product (and any other applicable Compounds) on its own or with a Third Party.

(b) Biogen's Option under Section 3.1 will expire and Ionis will be free to Develop and Commercialize the applicable Collaboration Product (and any other applicable Compounds) on its own or with a Third Party.

(c) Neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the terminated Neurology Targets and Collaboration Program(s).

(d) To the extent requested by Ionis, Biogen will promptly (1) assign to Ionis any manufacturing agreements with a CMO identified by Ionis to which Biogen is a party, solely to the extent such manufacturing agreements relate to the terminated Collaboration Program and (2) 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 under the terminated Collaboration Program(s) in the possession of Biogen and its contractors to the extent such data, results and information were generated by or on behalf of Biogen under this Agreement; and Ionis will pay all out-of-pocket direct Third Party costs and expenses in transferring such data, results and information together with Biogen's FTE Cost in transferring such data, results and information.

(e) If Biogen terminates this Agreement for convenience with respect to a Collaboration Program after the 30th day following Biogen's receipt of the Development Candidate Data Package for such Collaboration Program, but prior to Option exercise for such Collaboration Program, then Biogen will [***].

(f) Except as explicitly set forth in Section 10.4.1(a), Section 10.4.1(b) or Section 10.4.1(c), Biogen will have no further rights and Ionis will have no further obligations with respect to each terminated Collaboration Program.

(g) If Biogen terminates this Agreement for convenience with respect to a Collaboration Program that is not an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, then solely with respect to such Collaboration Program:

(i) Biogen will, and does hereby, grant to Ionis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, to all Biogen Technology Controlled by Biogen as of the date of such reversion that Covers the applicable Discontinued Collaboration Product(s) solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the applicable Discontinued Collaboration Product(s) in the Field (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*); and

(ii) Within [***] days following the date of the termination, Biogen will assign, and hereby does assign, to Ionis all of Biogen's right, title and interest in and to all Regulatory Materials, including any IND and orphan drug designation that relate to the applicable Discontinued Collaboration Product(s), *provided that*, (x) notwithstanding the foregoing, and subject to the provisions of Section 2.1, the Parties acknowledge that Biogen shall be permitted to use excerpts or portions of any such assigned Regulatory Materials in any other regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction related to products under the Ionis/Biogen Additional Agreements or products that do not include an oligonucleotide as an active pharmaceutical ingredient, *provided, further* that, for such products that do not include an oligonucleotide as an active pharmaceutical ingredient, such excerpts or portions shall not include any Confidential Information of Ionis, and (y) for clarity, such assignment of Biogen's right, title and interest in and to such Regulatory Materials shall not include the assignment of any Know-How (including any data) contained therein. If Biogen intends to use any excerpt or portion of any such assigned Regulatory Materials in accordance with clause (x) of the preceding sentence, Biogen shall, at least [***] days in advance of the anticipated submission of such excerpt or portion to a Regulatory Authority, notify Ionis of such intent and provide to Ionis a copy of such proposed excerpt or portion for review and comment. The Parties shall discuss in good faith any comments of Ionis with respect to such proposed excerpt or portion prior to submission thereof.

(h) If Biogen terminates this Agreement for convenience with respect to an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, then solely with respect to such Collaboration Program:

(i) Biogen will, and does hereby, grant to Ionis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, to all Biogen Technology Controlled by Biogen as of the date of such reversion that Covers the applicable Discontinued Collaboration Product(s) solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the applicable Discontinued Collaboration Product(s) in the Field (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*);

(ii) Within [***] days following the date of the termination, Biogen will transfer to Ionis for use with respect to the Development and Commercialization of the applicable Discontinued Collaboration Product(s), any Know-How, data, results and copies of Regulatory Materials in the possession of Biogen as of the date of such reversion to the extent related to such Discontinued Collaboration Product(s), and any other information or material specified in Section 4.9, *provided that*, for the avoidance of doubt, as between the Parties, title to any intellectual property that is Biogen Technology within any of the foregoing will remain with Biogen subject to the license granted to Ionis under Section 10.4.3(h)(i);

(iii) Within [***] days following the date of the termination, Biogen will assign, and hereby does assign, to Ionis all of Biogen's right, title and interest in and to all Regulatory Materials, including any IND and orphan drug designation that relate to the applicable Discontinued Collaboration Product(s), *provided that*, (x) notwithstanding the foregoing, and subject to the provisions of Section 2.1, the Parties acknowledge that Biogen shall be permitted to use excerpts or portions of any such assigned Regulatory Materials in any other regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction related to products under the Ionis/Biogen Additional Agreements or products that do not include an oligonucleotide as an active pharmaceutical ingredient, *provided, further* that, for such products that do not include an oligonucleotide as an active pharmaceutical ingredient, such excerpts or portions shall not include any Confidential Information of Ionis, and (y) for clarity, such assignment of Biogen's right, title and interest in and to such Regulatory Materials shall not include the assignment of any Know-How (including any data) contained therein. If Biogen intends to use any excerpt or portion of any such assigned Regulatory Materials in accordance with clause (x) of the preceding sentence, Biogen shall, at least [***] days in advance of the anticipated submission of such excerpt or portion to a Regulatory Authority, notify Ionis of such intent and provide to Ionis a copy of such proposed excerpt or portion for review and comment. The Parties shall discuss in good faith any comments of Ionis with respect to such proposed excerpt or portion prior to submission thereof; and

(iv) To the extent requested by Ionis, Biogen will promptly assign to Ionis any manufacturing agreements solely to the extent related to the applicable Discontinued Collaboration Products and identified by Ionis to which Biogen is a party.

10.4.4. **Termination After License Grant**. If this Agreement is terminated by a Party in accordance with this ARTICLE 10 after Biogen has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) for a particular Product, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to any Product or Collaboration Program that is the subject of such termination:

(a) The applicable licenses granted by Ionis to Biogen under this Agreement will terminate. Biogen, its Affiliates and Sublicensees will cease selling the applicable Products, unless Ionis elects to have Biogen continue to sell the applicable Products as part of the Transition Services to the extent provided in Section 10.4.6.

(b) Neither Party will have any further obligations under Section 2.1 of this Agreement with respect to the terminated Product, Neurology Target and Collaboration Program(s).

(c) Except as explicitly set forth in Section 10.4.1(a), Biogen will have no further rights and Ionis will have no further obligations with respect to the terminated Product, Neurology Target and Collaboration Program(s).

(d) If (i) Biogen terminates the Agreement under Section 10.2.1 (Biogen's Termination for Convenience) or (ii) Ionis terminates this Agreement under Section 10.2.4(b) (Ionis' Right to Terminate) or Section 10.2.5 (Remedies for Failure to Use Commercially Reasonable Efforts), then the following additional terms will also apply *solely with respect to the terminated Products and/or Collaboration Program(s)*:

(i) Biogen will, and does hereby, grant to Ionis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, to all Biogen Technology Controlled by Biogen as of the date of such reversion that Covers the applicable Discontinued Collaboration Product(s) solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the applicable Discontinued Collaboration Product(s) in the Field (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*);

(ii) Within [***] days following the date of the termination, Biogen will assign back to Ionis any Product-Specific Patent Rights and Ionis' interest in any Program Patents that relate to the applicable Biogen Alternate Modality Product(s) and/or Discontinued Collaboration Product(s) previously assigned by Ionis to Biogen under this Agreement;

(iii) Within [***] days following the date of the termination, Biogen will transfer to Ionis solely for use with respect to the Development and Commercialization of the applicable Discontinued Collaboration Product(s), any Know-How, data, results and copies of Regulatory Materials in the possession of Biogen as of the date of such reversion to the extent related to such Discontinued Collaboration Product(s), and any other information or material specified in Section 4.9, *provided that*, for the avoidance of doubt, as between the Parties, title to any intellectual property that is Biogen Technology within any of the foregoing will remain with Biogen subject to the license granted to Ionis under Section 10.4.4(d)(i), except as otherwise provided in Section 10.4.4(d)(iv) below;

(iv) Within [***] days following the date of the termination, Biogen will assign, and hereby does assign, to Ionis all of Biogen's right, title and interest in and to all Regulatory Materials, including any NDA, IND and orphan drug designation that relate to the applicable terminated Product(s), *provided that*, (x) notwithstanding the foregoing, and subject to the provisions of Section 2.1, the Parties acknowledge that Biogen shall be permitted to use excerpts or portions of any such assigned Regulatory Materials in any other regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction related to products under the Ionis/Biogen Additional Agreements or products that do not include an oligonucleotide as an active pharmaceutical ingredient, *provided, further* that, for such products that do not include an oligonucleotide as an active pharmaceutical ingredient, such excerpts or portions shall not include any Confidential Information of Ionis, and (y) for clarity, such assignment of Biogen's right, title and interest in and to such Regulatory Materials shall not include the assignment of any Know-How (including any data) contained therein. If Biogen intends to use any excerpt or portion of any such assigned Regulatory Materials in accordance with clause (x) of the preceding sentence, Biogen shall, at least [***] days in advance of the anticipated submission of such excerpt or portion to a Regulatory Authority, notify Ionis of such intent and provide to Ionis a copy of such proposed excerpt or portion for review and comment. The Parties shall discuss in good faith any comments of Ionis with respect to such proposed excerpt or portion prior to submission thereof;

(v) Biogen will, and does hereby, exclusively license to Ionis any trademarks that are specific to a Discontinued Collaboration Product(s) solely for use with such Discontinued Collaboration Product(s), in accordance with Section 4.1.6, *mutatis mutandis*; *provided, however*, in no event will Biogen have any obligation to license to Ionis any trademarks used by Biogen both in connection with the Product and in connection with the sale of any other product or service, including any BIOGEN- or BIOGEN-formative marks;

(vi) Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Program Patents arising from the terminated Product and/or Collaboration Program, and Biogen will provide Ionis with (and will instruct its counsel to provide Ionis with) all of the information and records in Biogen's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Program Patents; *provided, however*, if Ionis intends to abandon any such Jointly-Owned Program Patents without first filing a continuation or substitution, then Ionis will notify Biogen of such intention at least [***] days before such Patent Right will become abandoned, and Biogen 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; and

(vii) Ionis will have the obligation to pay royalties to Biogen under Section 6.12 with respect to the applicable Discontinued Collaboration Product(s). Such payments will be governed by the financial provisions in Section 6.14, and the definition of Net Sales will apply to sales of Discontinued Collaboration Product(s) by Ionis, in each case *mutatis mutandis*.

(e) With respect to Discontinued Collaboration Products, if Ionis terminates this Agreement due to Biogen's material breach or Biogen terminates this Agreement for convenience, upon Ionis' written request pursuant to a mutually agreed supply agreement, Biogen will sell to Ionis any bulk API, Clinical Supplies and Finished Drug Product in Biogen's possession at the time of such termination, at a price equal to [***].

(f) To the extent requested by Ionis, Biogen will promptly assign to Ionis any manufacturing agreements solely to the extent related to the applicable Discontinued Collaboration Products and identified by Ionis to which Biogen is a party.

(g) If Biogen under Section 10.2.1 or Section 10.2.2 voluntarily terminates its license under Section 4.1.1(b) with respect to a High Interest Target Biogen designated as a Biogen Alternate Modality Target then Section 2.1.1(f) will apply.

10.4.5. Remedies Available to Biogen for Ionis' Material Breach After Option Exercise.

(a) **Termination of Committees and Information Sharing**. If, after Option exercise, Ionis materially breaches this Agreement and fails to cure such breach within the time periods set forth under Section 10.2.4(a), and Biogen does not wish to terminate this Agreement in its entirety (an "***Ionis Breach Event***"), then, in addition to any other remedies Biogen may have under this Agreement or otherwise, Biogen will have the right to do any or all of the following in Biogen's discretion *solely with respect to the Collaboration Programs that are the subject of the Ionis Breach Event*:

(i) Terminate Ionis' right to participate in the CSC, Neurology JRC, the applicable Neurology JDC, JPC and any other subcommittees or working groups established pursuant to this Agreement;

(ii) Terminate Ionis' participation in any ongoing research and development programs under the applicable Collaboration Program and Biogen's funding obligations associated therewith;

(iii) Solely make all decisions required or permitted to be made by such committees or the Parties collectively under this Agreement in connection with the Development and Commercialization of the applicable Collaboration Product; *provided*, *however*, that Biogen will not have the right to create any obligations or incur any liabilities for or on behalf of Ionis;

(iv) Exclude Ionis from all discussions with Regulatory Authorities regarding applicable Products, *except* to the extent Ionis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law;

(v) Terminate Biogen's obligation to make further disclosures of Know-How or other information to Ionis pursuant to this Agreement related to the applicable Collaboration Products, including pursuant to Section 4.9 and Section 5.2.7, other than reports required by Section 6.14.1, Section 10.4.4 (if applicable), and as reasonably required to permit Ionis to perform its obligations under this Agreement; *provided* such remedy will not limit or diminish the scope of any licenses granted by Biogen to Ionis under this Agreement; and

(vi) If Ionis has not completed the Development activities that are its responsibility under the applicable ASO Development Candidate Identification Plan and Initial Development Plan, then Biogen may, but will not be obligated to, assume all responsibility for all such Development activities that would have otherwise been Ionis' responsibility under this Agreement.

Ionis will cooperate with the foregoing and provide to Biogen and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Biogen in assuming complete responsibility for the Development and Manufacture of the applicable Products in an efficient and orderly manner.

(b) **Biogen's Right of Setoff**. If there is [***] and Biogen does not wish to [***], then, in addition to any other remedies Biogen may have under this Agreement or otherwise, Biogen may setoff against any amounts owed to Ionis pursuant to ARTICLE 6 (Financial Provisions) *solely* with respect to the Collaboration Program that is the subject of the Ionis Breach Event [***] (the "***Setoff Amount***"). If Biogen exercises its setoff right under this Section 10.4.5(b), Biogen will provide Ionis with a written certificate, signed by Biogen's Chief Financial Officer, certifying that the amount setoff by Biogen represents [***]. Notwithstanding the foregoing, if Ionis notifies Biogen in writing (a "***Setoff Dispute Notice***") that it disputes Biogen's assertion that Ionis is in material breach of this Agreement or the amount setoff by Biogen (a "***Setoff Dispute***"), then (i) both Parties will participate in the dispute resolution process set forth on SCHEDULE 10.4.5(b), and (ii) pending the Parties' agreement regarding the appropriate setoff (if any) or a determination by the Advisory Panel of the proper amount that Biogen may setoff (if any) in accordance with SCHEDULE 10.4.5(b), Biogen will pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank. If the Parties cannot settle their dispute by mutual agreement, then, in accordance with SCHEDULE 10.4.5(b) the Advisory Panel will determine (1) the amount (if any) that Biogen may setoff against future payments *solely* with respect to the Collaboration Program that is the subject of the Ionis Breach Event to Ionis going forward, and (2) whether any portion of the escrow account should be released to Ionis or returned to Biogen, *provided* that any decision or determination by the Advisory Panel (a "***Panel Decision***") will not be treated as an arbitral award but will be binding on the Parties until and unless a court of competent jurisdiction (the "***Trial Court***") has determined in a judgment regarding some or all of the issues decided in the Panel Decision, and in any Action contemplated by the next sentence hereof the Trial Court will determine the facts and the law *de novo*, and will give a Panel Decision only such persuasive effect, if any, that after review of all of the facts and the law presented to the Trial Court by the Parties, the Trial Court deems appropriate, *provided* that the escrow agent will comply with a Panel Decision that determines that any portion of the escrow account should be released to Ionis or returned to Biogen. If it is determined in a judgment by the Trial Court that Ionis owes Biogen any damages, then, during the pendency of any appeal of the Trial Court's decision (or, if the Trial Court's decision is not appealed, until Biogen recoups such amount), Biogen may setoff against any future payments *solely* with respect to the Collaboration Programs that are the subject of the Ionis Breach Event to Ionis under this Agreement the amount of any such damages not paid by Ionis. If it is determined in a Trial Court that Biogen has setoff an amount that exceeds the amount of losses, damages and expenses actually incurred by Biogen as a result of Ionis' breach of this Agreement, then Biogen will promptly pay Ionis the amount of such excess, plus interest on such amount as provided for in Section 6.17 (Interest on Late Payments), with interest accruing from the time Biogen applied such excess setoff. If, with respect to a Setoff Dispute, Ionis provides a Setoff Dispute Notice to Biogen and Biogen fails to do any of the following: (X) appoint a member of the Advisory Panel to the extent required in Section 2 of SCHEDULE 10.4.5(b); (Y) meet with the Advisory Panel as required in Section 3 of SCHEDULE 10.4.5(b); or (Z) pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank, then Biogen will forfeit its right to set off under this Section 10.4.5(b) and SCHEDULE 10.4.5(b) with respect to any and all Setoff Disputes.

10.4.6. Transition Services.

(a) In the case where (i) Biogen terminates the Agreement under Section 10.2.1 (Biogen's Termination for Convenience) or (ii) Ionis terminates this Agreement under Section 10.2.4(b) (Ionis' Right to Terminate) or Section 10.2.5 (Remedies for Failure to Use Commercially Reasonable Efforts) with respect to one or more Products, the Parties wish to provide a mechanism to ensure that patients who were being treated with the Product prior to such termination or who desire access to the Product can continue to have access to such Product while the regulatory and commercial responsibilities for the Product are transitioned from Biogen to Ionis. As such, Ionis may request Biogen perform transition services as listed on SCHEDULE 10.4.6 and such other transition services that the Parties mutually agree in writing to (1) provide patients with continued access to the applicable Products, (2) transition the responsibilities under all Approvals and ongoing clinical studies for the applicable Product to Ionis or its designee, and (3) transition the then-current supply process and responsibilities for the Product to Ionis or its designee (collectively, the "***Transition Services***"). Subject to the Parties agreeing on a transition plan as described in Section 10.4.6(b), Biogen will perform such Transition Services using reasonable efforts for a period not to exceed [***] months from the termination date; *provided* that Biogen and Ionis may mutually agree to conduct the Transition Services for a longer period of time.

(b) Ionis may elect to have Biogen perform the Transition Services by providing written notice to Biogen no later than [***] days following the effective date of the termination. If Ionis requests Transition Services, then Ionis shall propose a transition plan setting forth the Transition Services to be performed by Biogen, including delivery and transition dates consistent with those set forth on SCHEDULE 10.4.6, and, for a period of [***] days after such request, the Parties will use good faith efforts to negotiate a mutually agreeable version of such transition plan. In addition, the Parties will, within [***] days after such request, establish a transition committee consisting of at least each Party's Alliance Managers, a representative from each Party's chemistry, manufacturing and controls (CMC) group who was responsible for the Product prior to the termination, and up to two additional representatives from each Party who are from other relevant functional groups to facilitate a smooth transition. While Biogen is providing Transition Services, Biogen and Ionis will mutually agree on talking points and a communication plan to customers, specialty pharmacies, physicians, regulatory authorities, patient advocacy groups, and clinical study investigators, and Biogen will make all such communication to such entities in accordance with the mutually agreed talking points.

(c) Ionis will pay Biogen for the Transition Services at [***] to perform the Transition Services, calculated [***]. In addition, Ionis will reimburse [***] to perform the Transition Services. Ionis will own all revenue derived from the Product after the termination date and Biogen will remit all such revenues to Ionis no later than the [***] day following the end of the month in which such revenue was received.

(d) Ionis or its designee will be sufficiently prepared to accept the transition of Development, Manufacturing and Commercialization activities with respect to the Products to Ionis or such designee on the timelines set forth on SCHEDULE 10.4.6 for the Transition Services. Biogen will have no liability under this Agreement with respect to a failure of or delay in the Transition Services to the extent caused by any failure or delay by Ionis or its designee in accepting the transition of Development, Manufacturing and Commercialization activities with respect to the Products. In the event that Biogen encounters any delays beyond Biogen's reasonable control, the Parties shall discuss in good faith and agree upon extended timelines for completion of the Transition Services.

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 Ionis and Biogen on February 28, 2011 (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. **Appointment of a Communications Lead**. Prior to the Initiation of each Clinical Study under the Initial Development Plan for any Collaboration Program for which Biogen has not yet been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) with respect to a Product, the Neurology JDC for such Collaboration Program shall appoint one of the Parties as the communications lead to take the lead role in drafting, coordinating and facilitating the public disclosure of data and results arising from such Clinical Study (the "***Communications Lead***"); *provided*, *however*, that (a) if a single Party is the IND-holder and sponsor of the Clinical Study, and is responsible for the conduct of the Clinical Study, then that Party shall automatically be deemed to be the Communications Lead and (b) if the applicable Neurology JDC cannot agree upon the designation of a Communications Lead, such matter shall be submitted to the CSC for resolution. The Communications Lead shall be responsible for drafting the initial publication and for coordinating and facilitating the disclosure activities for such Clinical Study as set forth in Sections 11.4.5 and 11.4.6; *provided, however*, that if, after having worked together in good faith, the Communications Lead and the other Party cannot agree on a matter related to the public disclosure of data and results arising from such a Clinical Study, then, subject to and without limiting Sections 11.4.5 and 11.4.6, (i) prior to Option exercise, Ionis will have final decision-making authority regarding such matter, and (ii) after Option exercise, Biogen will have final decision-making authority regarding such matter.

11.4.2. **Public Announcements**. On or promptly after the Effective Date, the Parties will jointly issue a public announcement of the execution of this Agreement in form and substance mutually agreed by the Parties. 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 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 11.4.11, 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 Biogen's sales projections) so the Parties may analyze the need for or desirability of publicly disclosing or reporting such event.

11.4.5. **Prior to License Grant**. Prior to the date Biogen has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) with respect to a Product, such Product is the sole property of Ionis and, subject to any communication plan for such Product mutually agreed to by the Parties in accordance with Section 1.10.2(d) and to the provisions of this Section 11.4.5 and Section 11.4.7, Ionis will have the sole right to issue press releases, publish, present or otherwise disclose the progress and results regarding such Product to the public, which shall be consistent with its practice with its other compounds and products; *provided that*, with respect to any proposed press release or other similar public communication by Ionis disclosing regulatory discussions, the efficacy or safety data or clinical results related to such Product, (i) Ionis will submit such proposed communication to Biogen for review at least two Business Days in advance of such proposed public disclosure, (ii) Biogen will have the right to review and recommend changes to such communication, and (iii) Ionis will in good faith consider any changes that are timely recommended by Biogen; and *provided further* that, if Biogen conducted or co-conducted a Clinical Study that is the subject of such public announcement, press release or other public disclosure, then any such public announcement, press release or other public disclosure shall be jointly issued by the Parties (unless Biogen expressly waives in writing its right to jointly issue such public announcement, press release or other public disclosure). If Biogen desires to make any public announcement, issue a press release or make any other public disclosure with respect to a Clinical Study that was conducted or co-conducted by Biogen prior to the date Biogen has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) with respect to a Product, Biogen shall so notify Ionis and shall provide Ionis with a draft thereof at least two Business Days prior to the proposed publication thereof. Ionis may review and provide comments to Biogen and the Parties shall discuss in good faith any such comments and seek to mutually agree on a final version of such proposed public announcement, press release or other public disclosure. Notwithstanding the foregoing, Ionis shall, pursuant to this Section 11.4.5, retain final decision-making authority over (x) whether such proposed public announcement, press release or other public disclosure shall be issued or made, and (y) the content thereof, and in no event shall Biogen issue any such public announcement, press release or other public disclosure under this Section 11.4.5 except in the final version approved by Ionis.

11.4.6. **After License Grant**. After the date Biogen has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) with respect to a Product, subject to the provisions of this Section 11.4.6 and Section 11.4.7, Biogen will have the sole right to issue press releases, publish, present or otherwise disclose the progress and results regarding such Product to the public, which shall be consistent with its practice with its other compounds and products; *provided* that with respect to any proposed press release or other similar public communication by Biogen disclosing regulatory discussions, the efficacy or safety data or results related to such Product or Biogen's sales projections, (i) Biogen will submit such proposed communication to Ionis for review at least two Business Days in advance of such proposed public disclosure, (ii) Ionis will have the right to review and recommend changes to such communication, and (iii) Biogen will in good faith consider any changes that are timely recommended by Ionis; and *provided further* that, if Ionis conducted or co-conducted a Clinical Study that is the subject of such public announcement, press release or other public disclosure, then any such public announcement, press release or other public disclosure shall be jointly issued by the Parties (unless Ionis expressly waives in writing its right to jointly issue such public announcement, press release or other public disclosure). If Ionis desires to make any public announcement, issue a press release or make any other public disclosure with respect to a Clinical Study that was conducted or co-conducted by Ionis, Ionis shall so notify Biogen and shall provide Biogen with a draft thereof at least two Business Days prior to the proposed publication thereof. Biogen may review and provide comments to Ionis and the Parties shall discuss in good faith any such comments and seek to mutually agree on a final version of such proposed public announcement, press release or other public disclosure. Notwithstanding the foregoing, Biogen shall, pursuant to this Section 11.4.6, retain final decision-making authority over (x) whether such proposed public announcement, press release or other public disclosure shall be issued or made, and (y) the content thereof, and in no event shall Ionis issue any such public announcement, press release or other public disclosure under this Section 11.4.6 except in the final version approved by Biogen.

11.4.7. **Resolution of Disagreements Regarding Public Announcements**. If the Parties cannot mutually agree on the need for or content of any press release, presentation or other public disclosure under Section 11.4.5 or Section 11.4.6 that is intended to be jointly issued, then either Party may promptly refer for resolution to a "C" level executive of each Party (e.g., a Party's Chief Operating Officer, Chief Executive Officer or Chief Business Officer) or to one of the Party's CSC members. During the at least two Business Day advance review period described in Section 11.4.5 or Section 11.4.6 (as applicable), such "C" level executives or CSC members will meet in person at a mutually acceptable time and location or by means of telephone or video conference to discuss in good faith and attempt to resolve such dispute.

11.4.8. **Scientific or Clinical Presentations for Collaboration Products**. Regarding any proposed scientific publications or public presentations related to summaries of results from any Clinical Studies generated by Ionis or Biogen for a Collaboration Product, the Parties acknowledge that scientific lead time is a key element of the value of the Collaboration Products under this Agreement and further agree to use Commercially Reasonable Efforts to control public scientific disclosures of the 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 [***] 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 Collaboration Programs. If, during such [***] 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 [***] 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 [***] 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. With respect to each Clinical Study, (a) if such Clinical Study is Initiated prior to the date Biogen has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) with respect to the applicable Product, Ionis shall determine authorship or attribution with respect to any proposed publications regarding the results of such Clinical Study, and (b) if such Clinical Study is Initiated after the date Biogen has been granted a license under Section 4.1.1(a) or Section 4.1.1(b) (as applicable) with respect to the applicable Product, Biogen shall determine authorship or attribution with respect to any proposed publications regarding the results of such Clinical Study, in each case ((a) and (b)), by interpreting and applying the authorship and attribution principles of the International Committee of Medical Journal Editors' *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals*, *provided* that (x) in each case, the Party that has the right to determine attribution or authorship in accordance with this Section 11.4.7 shall consider in good faith any reasonable comments timely made by the other Party with respect thereto, (y) any determination of authorship or attribution under this Section 11.4.7 shall be in compliance with the requirements of the applicable journal of the proposed publication, and (z) the Party that does not have the right to determine attribution or authorship in accordance with this Section 11.4.7 for any such proposed publication will have the right to have at least one author listed in such publication if such Party conducted or co-conducted such Clinical Study.

11.4.9. **SEC Filings**. Each Party will give the other Party a reasonable opportunity to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing.

11.4.10. **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.

11.4.11. **Acknowledgment**. Each Party will acknowledge in any press release, public presentation or publication regarding the Collaboration or a Product, the other Party's role in discovering and developing the Product or Discontinued Collaboration Product, as applicable, that the Product is under license from Ionis and otherwise acknowledge the contributions from the other Party, and each Party's stock ticker symbol (e.g., Nasdaq: IONS, BIIB).

(a) Biogen understands and acknowledges the importance to Ionis of continuing to be associated with the drugs it discovers under the Collaboration. As such, Biogen agrees that it will use reasonable efforts to prominently acknowledge Ionis' role in the discovery of a Product in any scientific, medical and other Product-related communications to the extent such communications address the research, discovery or commercialization of a Product, by prominently including the words "*Discovered by Ionis*" or equivalent language (collectively, the "***Ionis Attribution Language***") in any such communications; *provided*, *however*, that Biogen shall have no obligation to include the Ionis Attribution Language in any of the following: (i) communications or materials where such inclusion would be prohibited by Applicable Laws or applicable Third Party institutional, corporate or other policies; (ii) communications that Biogen does not control, such as publications with non-Biogen lead authors; (iii) materials primarily focused on or directed to patients, or other materials where Biogen branding is not prominently featured; or (iv) abstracts or other communications with a word limitation, if Biogen reasonably determines that such word limitation would preclude the inclusion of the Ionis Attribution Language, *provided that*, in each case Biogen will use reasonable efforts to have the Ionis Attribution Language included in any such communication, consistent with the efforts that Biogen uses to have statements regarding its own contributions to the Product included in such communication.

(b) Ionis may include the Product (and identify Biogen as its partner for the Product) in Ionis' drug pipeline.

ARTICLE 12.
MISCELLANEOUS

12.1. Dispute Resolution.

12.1.1. Escalation. In the event of any Dispute (other than a Setoff Dispute, which Setoff Dispute will be resolved pursuant to Section 12.1.3, or dispute regarding the construction, validity or enforcement of either Party's Patent Rights, which disputes will be resolved pursuant to Section 12.2), either Party may, within [***] days after either Party notifies the other Party that the Dispute has not been resolved (*provided, that* such notice cannot be given less than [***] days after the Dispute has arisen), make a written request that the Dispute be referred for resolution to the Executive Vice President, Business Development of Biogen and the Chief Operating Officer of Ionis (the "***Executives***"). Within [***] days of either Party's written request that the Dispute be referred to the Executives, the Executives will meet in person at a mutually acceptable time and location or by means of telephone or video conference to negotiate a settlement of a Dispute. Each Party may elect to have such Party's CSC representatives participate in such meeting, if desired, *provided* that it provides the other Party with reasonable advance notice of such intent so as to enable the other Party to have its CSC representatives also participate in such meeting, if desired. If the Executives fail to resolve the Dispute within such [***] day period, then the Dispute will be referred to mediation under Section 12.1.2.

12.1.2. Mediation. If a Dispute subject to Section 12.1.1 cannot be resolved pursuant to Section 12.1.1, or if neither Party timely makes the written request that the Dispute be referred to the Executives, the Parties will resolve any such Dispute in accordance with the dispute resolution procedures set forth in SCHEDULE 12.1.2.

12.1.3. Setoff Disputes. Setoff Disputes will be resolved in accordance with Section 10.4.5(b) and SCHEDULE 10.4.5(b).

12.1.4. Expert Resolution. In the event that a matter is referred for expert resolution under this Section 12.1.4 pursuant to Section 1.10.2(d) or under APPENDIX 3, the matter will be resolved by a panel of three (3) industry experts experienced in the issues comprising such dispute. One expert will be chosen by Ionis, one expert will be chosen by Biogen and the third expert will be chosen by mutual agreement of the experts chosen by Ionis and Biogen. The place of such expert resolution will be in Chicago, Illinois. Within [***] days after the selection of the third expert (which will occur not later than [***] days after a Party notifies the other Party that it elects to have a dispute resolved pursuant to this Section 12.1.4), the Parties will each simultaneously submit to the expert panel and one another a written statement of their respective positions on the relevant dispute. Each Party will have [***] days from receipt of the other Party's submission to submit a written response thereto, which will include any scientific and technical information in support thereof. The expert panel will conduct at least one hearing at which each Party will have the opportunity to advocate its position before the other Party and the expert panel. The expert panel will have the right to further meet with both Parties together, as necessary to make a determination. There will be no *ex parte* communications between an individual Party and either the expert panel or one or more experts. All documents submitted will be in the English language. Further, the expert panel will have the right to request information and materials and to require and facilitate discovery as it will determine is appropriate in the circumstances, taking into account the needs of the Parties and the desirability of making discovery expeditious and cost-effective determinations. No later than 90 days after the designation of the third expert or as otherwise agreed by the Parties, the expert panel will make a determination. The expert panel will provide the Parties with a written statement setting forth the basis of the determination in connection therewith. The decision of the expert panel will be final, binding and conclusive, absent manifest error. Each Party will bear its attorneys' fees, costs and disbursements (including, for example, expert witness fees and expenses, photocopy charges, travel expenses, etc.) and the Parties will share equally (50/50) the fees and costs of the expert panel. Judgment upon any award rendered pursuant to this Section 12.1.4 may be entered by any court having jurisdiction over the Parties' assets. Except to the extent necessary to confirm or enforce an award or as may be required by law, neither Party nor any of the experts may disclose the existence, content or results of any proceeding under this Section 12.1.4 without the prior written consent of both Parties.

12.2. Governing Law; Jurisdiction; Venue; Service of Process.

12.2.1. This Agreement and any Dispute will be governed by and construed and enforced in accordance with the laws of the State of Delaware, U.S.A., without reference to conflicts of laws principles.

12.2.2. Subject to the provisions of Section 12.1, each Party by its execution hereof, (a) hereby irrevocably submits to the exclusive jurisdiction of the United States District Court for the District of Delaware (or, if but only if such court lacks, or will not exercise, subject matter jurisdiction over the entirety of a Dispute, the Court of Chancery of the State of Delaware, or, if but only if such court lacks, or will not exercise, subject matter jurisdiction over the entirety of a Dispute, the Superior Court of the State of Delaware, with respect to the Dispute) for the purpose of any Dispute arising between the Parties in connection with this Agreement (each, an "***Action***") and (b) hereby waives to the extent not prohibited by Applicable Law, and agrees not to assert, by way of motion, as a defense or otherwise, in any such Action, any claim that it is not subject personally to the jurisdiction of the above-named courts, that venue in the above-named courts is improper, that its property is exempt or immune from attachment or execution, that any such Action brought in the above-named courts should be dismissed on grounds of forum non conveniens, should be transferred or removed to any court other than the above-named courts, or should be stayed by reason of the pendency of some other proceeding in any other court other than the above-named courts, or that this Agreement or the subject matter hereof may not be enforced in or by such courts and (c) hereby agrees not to commence any such Action other than before the above-named courts. Notwithstanding the previous sentence, a Party may commence any Action in a court other than the above-named court solely for the purpose of enforcing an order or judgment issued by the above-named court.

12.2.3. Each Party hereby agrees that service of process: (a) made in any manner permitted by Delaware law, or (b) made by overnight express courier service (signature required), prepaid, at its address specified pursuant to Section 12.7, will constitute good and valid service of process in any such Action and (c) waives and agrees not to assert (by way of motion, as a defense, or otherwise) in any such Action any claim that service of process made in accordance with clause (a) or (b) does not constitute good and valid service of process.

12.3. **Remedies**. Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary restraining order or a preliminary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Agreement, and the Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive relief would be appropriate. 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 6.13.3(c)). Except for the offsets and credits explicitly set forth in Section 1.8.3, Section 6.15, Section 6.13.3(b), Section 6.13.3(d) and Section 10.4.5(b), neither Party will have the right to setoff 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 consent of the other, which will not be unreasonably withheld, delayed or conditioned, except that each Party may assign this Agreement and the rights, obligations and interests of such Party, in whole or in part, without the other Party's consent, to any of its Affiliates, to any 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; *provided*, if Biogen transfers or assigns this Agreement to [***] described in this Agreement, then Biogen (or such Affiliate), will [***] due Ionis under ARTICLE 6 for the [***] assignment. In addition, Ionis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without Biogen's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction. Any purported assignment or transfer made in contravention of this Section 12.4 will be null and void.

The [***].

To the extent Ionis utilizes a [***] in any year, Ionis will [***] to Biogen [***]. To assist Biogen in determining when a refund is due from Ionis pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which Biogen [***] payment under this Section 12.4, and each year thereafter (including, for clarity, all years in which Ionis utilizes a [***], Ionis will provide Biogen with Ionis' Annual tax returns (federal and state) and, in years in which Ionis utilizes [***], supporting documentation for such [***]. Notwithstanding the foregoing, if the [***].

12.5. Change of Control.

12.5.1. Research Activities. If, at any time during the Research Term, a Change of Control occurs, then at any time prior to the [***] anniversary of the closing of such Change of Control, upon written notice to Ionis, Biogen may either:

(a) Extend the Research Term until such time as Ionis has completed target validating activities that are Ionis Activities under the Neurological Disease Research Plan for a total of [***] High Interest Targets;

(b) Terminate the Research Term, in which case: (i) Ionis will complete all ongoing target validation work that are Ionis Activities under the Neurological Disease Research Plan and advance each such target to Target Sanction (but for clarity, no target validation work will be initiated for any new target under the Neurological Disease Research Plan); (ii) Ionis will complete all ongoing Ionis Activities under the Core Research Plan (but for clarity, no new work will be initiated under the Core Research Plan); (iii) for each Collaboration Target that is not an ALS Target that reaches Target Sanction or each ALS Target designated a Collaboration Target, an ASO Development Candidate Identification Plan will be prepared and Ionis will carry out its obligations under such plan, all in accordance with Section 1.10.1; (iv) Ionis will continue to perform its obligations under each ongoing ASO Development Candidate Identification Plan until the end of the applicable ASO Development Candidate Identification Term and under each ongoing Initial Development Plan until completion of all Ionis Activities thereunder; (v) for each Collaboration Program for which a Development Candidate is identified as provided herein, Biogen may, upon written notice to Ionis, such notice to be delivered within [***] days after designating a Development Candidate for the applicable Collaboration Program, elect to either (A) exercise the applicable Option by notifying Ionis in writing of Biogen's election to license the Collaboration Product [***] and will be paid to Ionis within [***] days after Biogen's election under clause (A) of this Section 12.5.1(b), and after such exercise, Biogen will not be obligated [***], or (B) establish an Initial Development Plan for such Collaboration Program pursuant to Section 1.10.2(d), in which case Ionis and Biogen will continue to exercise their rights and perform their respective obligations with respect to the applicable Collaboration Program under the terms of this Agreement; (vi) the Research Term will end upon Ionis' completion of all Ionis Activities under clauses (i), (ii) and (iii) above; and (vii) within [***] days after the end of the Research Term, Ionis will [***]; or

(c) Allow such [***] period to lapse without providing any such notice of election under this Section 12.5.1, in which case Ionis and Biogen will continue to exercise their rights and perform their respective obligations under the terms of this Agreement.

12.5.2. **Collaboration Programs.** On a Collaboration Program-by-Collaboration Program basis, if, at any time during the Option Period, a Change of Control occurs involving Ionis and a Person that, at the time of the close of such Change of Control, is developing in human clinical trials or commercializing a Directly Competitive Collaboration Product within the Field or is engaged in a Directly Competitive Collaboration Program (such pre-existing Directly Competitive Collaboration Product, a "***Pre-Existing Competitive Product***") or, at any time during the Term after the closing of such Change of Control, develops or acquires a Directly Competitive Collaboration Product or begins a Directly Competitive Collaboration Program (such Person being hereinafter referred to as a "***Competing Collaboration Acquirer***") and such Competing Collaboration Acquirer has not, within [***] of either (i) the closing of the Change of Control in the event the Directly Competitive Collaboration Product is being developed in human clinical trials or commercialized, or the Directly Competitive Collaboration Program exists, as of such closing date or (ii) the date of first development or acquisition of such Directly Competitive Collaboration Product or the date on which such Competing Collaboration Acquirer begins such Directly Competitive Collaboration Program (the "***Collaboration Divestiture Period***") divested itself of the Directly Competitive Collaboration Product or Directly Competitive Collaboration Program, or terminated development and commercialization of such Directly Competitive Collaboration Product or such Directly Competitive Collaboration Program, then (A) Ionis will provide written notice to Biogen of the closing of such Change of Control or Collaboration Divestiture Period, as applicable, (B) [***], (C) solely with respect to any Collaboration Program that relates to such Directly Competitive Collaboration Product or Directly Competitive Collaboration Program for which Initiation of IND-Enabling Toxicology Studies have not occurred, subject to Section 12.5.3, elect to have Ionis complete Ionis Activities under this Agreement for such Collaboration Program until such time as the applicable Collaboration Program is ready to begin IND-Enabling Toxicology Studies, after which Biogen may elect to exercise its rights under clause (D) of this Section 12.5.2 with respect to such Collaboration Program (in which case the applicable deadline for Biogen's notice under such clause will be extended until [***] after designation of a Development Candidate for such Collaboration Program), and (D) solely with respect to any Collaboration Product affected by such Directly Competitive Collaboration Product or Directly Competitive Collaboration Program, Biogen will have the right, within [***] following such written notice, to either:

(a) if unexercised, exercise the applicable Option by notifying Ionis in writing of Biogen's election to license the Collaboration Product at a prorated license fee payment as compared to the license fee payment set forth in Section 6.5, based upon the stage of Development of the applicable Collaboration Product at the time of Change of Control or Collaboration Divestiture Period, as applicable, which license fee payments are set forth on TABLE A of SCHEDULE 12.5 hereto. If Biogen exercises the applicable Option pursuant to this Section 12.5.2(a), Biogen will not be obligated [***]. Upon Biogen's exercise of its Option pursuant to this Section 12.5.2(a), Biogen will be deemed to have obtained and Ionis will be deemed to have granted the license set forth in Section 4.1.1; or

(b) Allow such [***] period to lapse without providing any such notice of election under this Section 12.5.2, or otherwise provide Ionis with written notice within such period electing not to exercise the applicable Option pursuant to Section 12.5.2(a) above, in either of which cases, subject to Section 12.5.3, Ionis and Biogen will continue to exercise their rights and perform their respective obligations with respect to the Collaboration Product under the terms of this Agreement.

Provided that Ionis complies with Section 12.5.3, Biogen's rights as set forth in this Section 12.5.2 shall be Biogen's exclusive remedies for the failure of a Competing Collaboration Acquirer to divest or terminate development and commercialization of a Directly Competitive Collaboration Product or Directly Competitive Collaboration Program during the Collaboration Divestiture Period in accordance with this Section 12.5.2, and the development or commercialization of a Pre-Existing Competitive Product by a Competing Collaboration Acquirer will not be a violation of Ionis' exclusivity covenants under Section 2.1.1. Upon Biogen's exercise of an Option pursuant to Section 12.5.2(a) above, Ionis will carry out its technology transfer obligations pursuant to Section 4.9 with respect to the Collaboration Product. For the avoidance of doubt, except as set forth in this Section 12.5.2, all other terms and conditions of this Agreement will apply to any such license granted pursuant to Biogen's exercise of its rights hereunder.

12.5.3. Protective Provisions. At any time while Ionis is conducting activities pursuant to Section 12.5.2, to separate its Development activities under this Agreement from development activities relating to a Directly Competitive Collaboration Product ("***Directly Competing Development Activities***"), Ionis will, and will cause the Competing Collaboration Acquirer to, (a) establish separate teams to conduct Development activities under this Agreement and such Directly Competing Development Activities, (b) prevent any Know-How that is Confidential Information relating to the Development of the applicable Collaboration Product from being disclosed to, or used by, individuals performing such Directly Competing Development Activities and (c) not use or reference any Know-How that is Confidential Information or conduct any activities Covered by any Patent Rights, in each case Controlled by Ionis or its Affiliates prior to the effective date of the Change of Control in the development, manufacture or commercialization of the Directly Competitive Collaboration Product.

12.5.4. **Biogen Alternate Modality Programs.** On a Biogen Alternate Modality Product-by-Biogen Alternate Modality Product basis, if, at any time during the Term, a Change of Control occurs involving Ionis and a Person that, at the time of the closing of such Change of Control, is developing in human clinical trials or commercializing a Directly Competitive Biogen Alternate Modality Product within the Field or is engaged in a Directly Competitive Biogen Alternate Modality Program or, at any time during the Term after such closing of the Change of Control, develops or acquires a Directly Competitive Biogen Alternate Modality Product or begins a Directly Competitive Biogen Alternate Modality Program (such Person being hereinafter referred to as a "***Competing Alternate Modality Acquirer***") and such Competing Alternate Modality Acquirer has not, within [***] of either (i) closing of the Change of Control in the event the Directly Competitive Biogen Alternate Modality Product is being developed in human clinical trials or commercialized, or the Directly Competitive Biogen Alternate Modality Program exists, as of such closing date or (ii) the date of first development or acquisition of such Directly Competitive Biogen Alternate Modality Product or the date on which such Competing Alternate Modality Acquirer begins such Directly Competitive Biogen Alternate Modality Program (the "***Alternate Modality Divestiture Period***") divested itself of the Directly Competitive Biogen Alternate Modality Product or Directly Competitive Biogen Alternate Modality Program, terminated development and commercialization of such Directly Competitive Biogen Alternate Modality Product or such Biogen Alternate Modality Program or assigned this Agreement pursuant to Section 12.4 to a Third Party that is not itself developing or commercializing a Directly Competitive Collaboration Product or engaged in a Directly Competitive Biogen Alternate Modality Program, then (i) Ionis will provide written notice to Biogen of the closing of such Change of Control or Alternate Modality Divestiture Period, as applicable, and (ii) [***]. For clarity, Biogen's rights as set forth in this Section 12.5.4 shall be Biogen's exclusive remedies for the failure of a Competing Alternate Modality Acquirer to divest or terminate development and commercialization of a Directly Competitive Biogen Alternate Modality Product or Directly Competitive Collaboration Program or assigned this Agreement to an applicable Third Party, in each case, during the Alternate Modality Divestiture Period in accordance with this Section 12.5.4.

12.6. **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.

12.7. **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 Ionis, addressed to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: Chief Operating Officer Fax: 760-918-3592
with a copy to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel Fax: 760-268-4922
If to Biogen, addressed to:	Biogen MA Inc. 14 Cambridge Center Cambridge, MA 02142 Attention: Senior Vice President Corporate Development Fax: 866-795-0181
with a copy to:	Ropes & Gray LLP Prudential Tower 800 Boylston Street Boston, MA 02199-3600 Attention: Marc A. Rubenstein, Esq. Fax: 617-235-0706

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.

12.8. **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, including the ALS Letter Agreement), amends and restates the Original Agreement, is a comprehensive and integrated statement of the agreement between the Parties with respect to the subject matter hereof and fully supersedes the Original Agreement for the period commencing on the Amendment Date and continuing thereafter. Without limiting the foregoing, this Agreement supersedes that certain side letter between the Parties, dated as of October 9, 2015, relating to drug substance process development and manufacturing, solely to the extent such side letter relates to Collaboration Programs under this Agreement. For clarity, such side letter shall remain in full force and effect with respect to the Ionis/Biogen Additional Agreements. For the avoidance of doubt, this Agreement in no way supersedes, modifies or otherwise affects any of the Ionis/Biogen Additional Agreements, which will remain in full force and effect in accordance with each of their respective terms. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties with respect to the subject matter hereof other than as set forth herein. 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 and Appendices hereto 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 and good laboratory and clinical practices and cGMP 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 Amendment Date.

BIOGEN MA INC.

By: /s/ John McDonald
Name: John McDonald
Title: Vice President, Business Development

SIGNATURE PAGE TO AMENDED AND RESTATED STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT 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 Amendment Date.

IONIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Chief Operating Officer

SIGNATURE PAGE TO AMENDED AND RESTATED STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

List of Appendices and Schedules

APPENDIX 1 – Definitions

APPENDIX 2 – Development Candidate Checklist

APPENDIX 3 – Multi-Indication Target Process

APPENDIX 4 – Form of Side Letter

SCHEDULE 1.1.4 – Biogen Conducted Non-ALS Targets

SCHEDULE 1.2.4 – Terms and Conditions for Provision of Research ASOs to Biogen

SCHEDULE 1.6.1 – ALS Letter Agreement

SCHEDULE 1.10.2(c) – Ionis' Standard IND-Enabling Toxicology Studies

SCHEDULE 1.10.2(d) – Initial Development Plan Requirements

SCHEDULE 1.10.2(d)(v) – Study Synopsis Requirements

SCHEDULE 1.10.2(e) – Apportionment of Certain Milestone Payments and Biogen-Approved Costs

SCHEDULE 1.10.6 – Ionis API Supply for ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs

SCHEDULE 1.18.1 – Collaboration Steering Committee Governance

SCHEDULE 1.18.2 – Neurology JRC Governance

SCHEDULE 1.18.3 – Neurology JDC Governance

SCHEDULE 1.18.6 – Alliance Management Activities

SCHEDULE 4.4.1(a) – Drug Substance Process and Formulation Development Activities

SCHEDULE 4.9.2(c) – Ionis' Fully Absorbed Cost of Goods Methodology

SCHEDULE 5.1.4 – Biogen's Development and Commercialization Activities

SCHEDULE 5.1.6 – Integrated Development Plan Content

SCHEDULE 6.10.2(e) – Royalty Calculation Examples

SCHEDULE 6.10.2(f) – Allocation of Net Sales

SCHEDULE 6.13.1 – Certain Ionis In-License Agreements

SCHEDULE 8.2.4(a) – Ionis Core Technology Patents

SCHEDULE 8.2.4(b) – Ionis Manufacturing and Analytical Patents

SCHEDULE 8.2.4(c) – Ionis Product-Specific Patents

SCHEDULE 8.2.8 – Prior Agreements

SCHEDULE 10.4.5(b) – Advisory Panel Regarding Setoff Disputes

SCHEDULE 10.4.6 – Transition Services

SCHEDULE 12.1.2 – Mediation

SCHEDULE 12.5 – Applicable License Fee Payments in Change of Control for Collaboration Products, and [***]

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"***Accelerated Target***" has the meaning set forth in Section 1.8.4.

"***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 Biogen 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 Market in the EU, (c) in any Major Market in Europe that is not a European Union country, receipt by Biogen of written notice of acceptance by the applicable Regulatory Authority of such MAA for filing in such country, and (d) in Japan, receipt by Biogen 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).

"***Action***" has the meaning set forth in Section 12.2.2.

"***Actual Biogen-Approved Costs***" has the meaning set forth in Section 1.14.1(e).

"***Additional Core IP***" means Third Party intellectual property that is necessary to [***]. For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***].

"***Additional Plan Costs***" means [***].

"***Advisory Panel***" has the meaning in SCHEDULE 10.4.5(b) of this Agreement.

"***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 Ionis 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 1.18.6.

"***ALS"*** means the disease amyotrophic lateral sclerosis.

"***ALS Collaboration Program***" means a Collaboration Program focused on an ALS Target.

"***ALS Option Deadline***" has the meaning set forth in Section 3.1.3.

"***ALS Pre-Licensing Milestone Event***" has the meaning set forth in Section 6.5.

"***ALS Target***" means the initial ALS-associated High Interest Targets identified as ALS Targets on SCHEDULE 1.2.3(a) on the Effective Date, plus any ALS-associated High Interest Target that is designated as an ALS Target in accordance with Section 1.2.3(a).

"***ALS Target List***" means the list of ALS-associated High Interest Targets identified as ALS Targets on the High Interest Target List. For clarity, at any given time, if a gene target is not on the ALS Target List at such time, then such gene target is not an ALS Target.

"***Alternate Modality***" means a therapeutic approach for a gene target that is not an oligonucleotide approach.

"***Alternate Modality Divestiture Period***" has the meaning set forth in Section 12.5.4.

"***Amendment Date***" has the meaning set forth in the Preamble of this Agreement.

"***ANDA***" means an Abbreviated New Drug Application and all amendments and supplements thereto filed with the FDA, or the equivalent application filed with any equivalent agency or governmental authority outside the U.S. (including any supra-national agency such as the EMA in the EU).

"***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 cGMP for a Collaboration 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 Biogen (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 an oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases long and that modulates expression or splicing of a gene target via the binding, partially or wholly, of such compound to the RNA of such gene target, excluding any double stranded oligonucleotide compounds that are designed to act through the RNA-induced silencing complex.

"***ASO Development Candidate Identification Plan***" has the meaning set forth in Section 1.10.1(a).

"***ASO Development Candidate Identification Term***" has the meaning set forth in Section 1.10.1(b).

"***Audit Report***" has the meaning set forth in Section 6.15.

"***Bankruptcy Code***" has the meaning set forth in Section 10.2.7(b).

"***Biogen***" has the meaning set forth in the Preamble of this Agreement.

"***Biogen Activities***" means, under any Neurology Plan, any and all research, pre-clinical and/or clinical activities that Biogen agrees to conduct; *provided* that Biogen will be deemed to have agreed to conduct any activities designated as Biogen Activities under any Neurology Plan it approves.

"***Biogen Alternate Modality Milestone Event***" has the meaning set forth in Section 6.3.

"***Biogen Alternate Modality Product***" means a finished drug product that contains a molecule that is (i) not an oligonucleotide, (ii) designed to bind, mimic or otherwise affect a protein or RNA that is encoded by a Biogen Alternate Modality Target, and (iii) discovered by Biogen or its Affiliates or any Third Party acting on their behalf.

"***Biogen Alternate Modality Program***" means a program to discover, Develop, Manufacture and Commercialize a Biogen Alternate Modality Product.

"***Biogen Alternate Modality Royalty***" has the meaning set forth in Section 6.9.1.

"***Biogen Alternate Modality Royalty Period***" has the meaning set forth in Section 6.9.2.

"***Biogen Alternate Modality Target***" is either (i) a High Interest Target that is designated as a Biogen Alternate Modality Target under Section 1.3, Section 1.4 or Section 1.8, (ii) a Collaboration Target that is changed to a Biogen Alternate Modality Target under Section 3.2.2, or (v) a Collaboration Target that is added as a Biogen Alternate Modality Target under Section 3.2.4.2.

"***Biogen-Approved Changes***" means any changes (including number of subjects, duration of dosing, additional studies, additional endpoints, additional analysis, etc.) to the applicable Neurology Plan for a Product that are requested by either Party after the Parties have set the initial Cost Estimates for such Neurology Plan under Section 1.10.2(e), and (i) required by a Regulatory Authority or (ii) agreed to be paid for by Biogen.

"***Biogen-Approved Costs***" has the meaning set forth in Section 1.14.1

"***Biogen Conducted Non-ALS Collaboration Program***" means a Collaboration Program focused on a Biogen Conducted Non-ALS Target.

"***Biogen Conducted Non-ALS Option Deadline***" has the meaning set forth in Section 3.1.3.

"***Biogen Conducted Non-ALS Target***" means each of the High Interest Targets listed on SCHEDULE 1.1.4, which may be updated by mutual written agreement of the Parties to include additional High Interest Targets relating to [***].

"***Biogen Full Royalty***" has the meaning set forth in Section 6.10.1.

"***Biogen Know-How***" means any Know-How owned, used, developed by, or licensed to Biogen or its Affiliates, in each case to the extent Controlled by Biogen or its Affiliates on the Effective Date or at any time during the Agreement Term, *but specifically excluding* the Biogen Program Know-How.

"***Biogen Manufacturing Program Patents***" has the meaning set forth in Section 4.9.3.

"***Biogen Patents***" means any Patent Rights included in the Biogen Technology.

"***Biogen Product-Specific Patents***" means all Product-Specific Patents owned, used, developed by, or licensed to Biogen or its Affiliates, in each case to the extent Controlled by Biogen or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***Biogen Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Biogen Program Patents***" has the meaning set forth in Section 7.1.2.

"***Biogen Program Technology***" has the meaning set forth in Section 7.1.2.

"***Biogen-Prosecuted Patents***" has the meaning set forth in Section 7.2.5(b).

"***Biogen Reduced Royalty***" has the meaning set forth in Section 6.10.2(c).

"***Biogen Results***" has the meaning set forth in Section 4.9.3.

"***Biogen Supported Pass-Through Costs***" means [***].

"***Biogen Technology***" means the Biogen Program Technology, Jointly-Owned Program Technology, Biogen Product-Specific Patents and any trademarks described in Section 4.1.6, owned, used, developed by, or licensed to Biogen or its Affiliates that is necessary or useful to Develop, register, Manufacture or Commercialize a Product.

"***Biogen's FTE Cost***" means the FTE Rate applicable to Biogen, *multiplied* by the applicable number of FTEs.

"***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.

"[***]" means [***], or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***Calendar Quarter***" means a period of three consecutive months ending on the last day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2013, the Effective Date) and ending on December 31.

"***Carryover Development Candidate***" has the meaning set forth in Section 1.10.1(e).

"***cGMP***" 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.

"***Change of Control***" means, with respect to Ionis, (a) a merger or consolidation of Ionis with a Third Party which results in the voting securities of Ionis outstanding immediately prior thereto ceasing to represent at least 50% of the combined voting power of the surviving entity immediately after such merger or consolidation, (b) a transaction or series of related transactions in which a Third Party, together with its Affiliates, becomes the owner of 50% or more of the combined voting power of Ionis' outstanding securities, (c) the sale or other transfer to a Third Party of all or substantially all of Ionis' business to which the subject matter of this Agreement relates, or (d) the stockholders or equity holders of Ionis will approve a plan of complete liquidation of Ionis or an agreement for the sale or disposition by Ionis of all or a substantial portion of its assets, other than pursuant to the transaction as described above or to an Affiliate. Notwithstanding the foregoing, the sale or issuance of shares in exchange for cash for purposes of a *bona fide* financing will not constitute a Change of Control.

"***Claims***" has the meaning set forth in Section 9.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Trial, Phase 2 Trial, Phase 3 Trial or Phase 4 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 Collaboration Product for use in a Clinical Study.

"***CMC***" has the meaning set forth in Section 1.13.1(c).

"***CMO***" means a Third Party contract manufacturer Manufacturing API, Clinical Supplies or Finished Drug Product for any purpose under this Agreement.

"***Collaboration***" means the conduct of the Neurology Plans in accordance with this Agreement.

"***Collaboration Divestiture Period***" has the meaning set forth in Section 12.5.2.

"***Collaboration Product***" means, on a Collaboration Program-by-Collaboration Program basis, a finished drug product containing a Compound as an active pharmaceutical ingredient.

"***Collaboration Program***" has the meaning set forth in Section 1.6.1.

"***Collaboration Target***" means a gene target for which the Parties wish to start an ASO drug discovery program that is either (i) a High Interest Target that is not an ALS Target and is designated as a Collaboration Target under Section 1.3 or Section 1.8, (ii) an ALS Target designated as a Collaboration Target under Section 1.5, (iii) an Ionis Neurology Target designated as a Collaboration Target under Section 1.4, (iv) a Biogen Alternate Modality Target that is changed to a Collaboration Target under Section 3.2.1, or (v) a Neurology Target that is added as a Collaboration Target under Section 3.2.4.1. As of the Effective Date [***] is a Collaboration Target that is an ALS Target and is not a Multi-Indication Target.

"***Collaborator IP***" has the meaning set forth in Section 7.1.3(b).

"***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) Biogen, with respect to a Product that is being Developed and Commercialized by or on behalf of Biogen, its Affiliates or Sublicensees hereunder, and (b) Ionis, with respect to a Discontinued Collaboration Product that is being Developed and Commercialized by or on behalf of Ionis, 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 Biogen's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to perform (i) any Biogen Activities in a Neurology Plan, and (ii) the "*General Activities*" described in SCHEDULE 5.1.4, and Commercially Reasonable Efforts as it applies to Ionis' Development of a Product hereunder includes use of Commercially Reasonable Efforts to adhere to the activities and timelines set forth in each Neurology Plan.

"***Communications Lead***" has the meaning set forth in Section 11.4.1.

"***Competing Alternate Modality Acquirer***" has the meaning set forth in Section 12.5.4.

"***Competing Collaboration Acquirer***" has the meaning set forth in Section 12.5.2.

"***Competitive Infringement***" has the meaning set forth in Section 7.5.1.

"***Compound***" means, on a Collaboration Program-by-Collaboration Program basis, any ASO that is designed to bind to the RNA that encodes the applicable Collaboration Target, where such ASO is discovered by Ionis prior to or in the performance of any Neurology Plan, including each Development Candidate under such Collaboration 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.

"***Conflicting Patent Right***" has the meaning set forth in Section 7.2.5(c).

"***Contracting Party***" has the meaning set forth in Section 1.10.7.

"***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 Ionis Supported Pass-Through Costs in the case of Ionis, and other than Biogen Supported Pass-Through Costs in the case of Biogen), 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.

"***Core Research Plan***" has the meaning set forth in Section 1.2.

"***Core Research Program***" has the meaning set forth in Section 1.2.

"***Cost Estimate***" has the meaning set forth in Section 1.10.2(e).

"***Cover***," "***Covered***" or "***Covering***" means, with respect to a patent, that, but for rights granted to a Person under such patent, the act of making, using or selling by such Person 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.

"***CSC***" has the meaning set forth in Section 1.18.1.

"***CTD***" has the meaning set forth in Section 4.5.

"***Deferral Notice***" has the meaning set forth in Section 1.8.1.

"***Deferral Period***" has the meaning set forth in Section 1.8.1.

"***Deferred Target***" has the meaning set forth in Section 1.8.1.

"***Deferred Target Development Candidate"*** means a Development Candidate identified in accordance with Section 1.8.4.

"***Deficiency Notice***" has the meaning set forth in Section 3.1.2.

"***Design Notice***" has the meaning set forth in Section 6.2.1.

"***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 Ionis' RMC in accordance with Ionis' standard procedures for designating development candidates [***] as ready to start IND-Enabling Toxicology Studies; *provided, however*, that with respect to any Primarily Neuro Multi-Indication Target, such Compound will be reasonably selected by Biogen (giving good faith consideration to the input of Ionis' representatives on the Neurology JRC) as a Development Candidate from the body of work Ionis used to determine the applicable Compound Ionis believes is ready to start IND-Enabling Toxicology Studies. The checklist Ionis 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 [***], the [***]; *provided* such package contains [***]. The checklist Ionis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 2.

"***Diagnostic Option***" has the meaning set forth in Section 3.3.1.

"***Directly Competing Development Activities***" has the meaning set forth in Section 12.5.3.

"***Directly Competitive Biogen Alternate Modality Product***" means with respect to a Biogen Alternate Modality Product, a product designed to bind to or directly modulate the Biogen Alternate Modality Target targeted by such Biogen Alternate Modality Program.

"***Directly Competitive Biogen Alternate Modality Program***" means any internal research program for which [***] or [***], with the goal of discovering and developing a Directly Competitive Biogen Alternate Modality Product for which drug discovery activities have been initiated.

"***Directly Competitive Collaboration Product***" means with respect to a Collaboration Product, any product, other than such Collaboration Product, that is designed to bind to or directly modulate the Collaboration Target targeted by such Collaboration Product.

"***Directly Competitive Collaboration Program***" means any internal research program for which [***] or [***], with the goal of discovering and developing a Directly Competitive Collaboration Product for which drug discovery activities have been initiated.

"***Disclosing Party***" has the meaning set forth in Section 11.1.

"***Discontinued Collaboration Product***" means a Collaboration Product that is the subject of a termination under this Agreement.

"***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.

"***DMPK Agreement***" means the DMPK Research, Development, Option and License Agreement between the Parties dated June 27, 2012, as amended and/or restated from time to time.

"***DOJ***" has the meaning set forth in Section 3.1.4(a).

"***Drug Development Program***" means the aggregate drug development activities related to each Development Candidate through completion of the first Phase 2 PoC Trial under a Collaboration Program in accordance with the applicable Initial Development Plan for all Collaboration Programs under this Agreement.

"***Effective Date***" has the meaning set forth in the Preamble of this Agreement.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"***Equal Multi-Indication Target***" has the meaning set forth in APPENDIX 3.

"***Estimated Biogen-Approved Costs***" means Ionis' good faith estimate of the Biogen-Approved Costs it will incur during the applicable Measurement Period.

"***Estimated Lock Date***" has the meaning set forth in Section 3.1.1.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union.

"***Excluded Payments***" means (i) royalty or profit sharing payments, or any other type of payment based on periodic sales of a Collaboration Product or Deferred Target Development Candidate; (ii) payments made in consideration of Ionis' or Ionis' Affiliate's equity or debt securities at fair market value; (iii) payments made to pay for or reimburse Ionis or Ionis' Affiliate for the fully-burdened cost of research and development; (iv) payments made to pay for or reimburse Ionis or Ionis' Affiliate for the cost of prosecuting, maintaining or defending Patent Rights; and (v) payments made to Ionis or Ionis' Affiliate to pass-through to a Third Party in satisfaction of a payment obligation Ionis or Ionis' Affiliate has to such Third Party.

"***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.

"[***]" means any form of the [***].

"***[***] Collaboration Program***" means an [***] Collaboration Program solely and exclusively focused on [***].

"***Field***" means, except as may be limited under Section 4.1.5, 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 Biogen, 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 2.2.1.

"***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 Ionis following exercise of the applicable Option by Biogen.

"***Follow-On Interest Notice***" has the meaning set forth in Section 2.2.1.

"***Follow-On Negotiation Notice***" has the meaning set forth in Section 2.2.1.

"***FTC***" has the meaning set forth in Section 3.1.4(a).

"***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 Costs***" has the meaning set forth in Section 1.14.1.

"***FTE Rate***" means $[***] for the Calendar Year 2013. The FTE Rate will be increased each Calendar Year thereafter by the [***].

"***Full Royalty Period***" has the meaning set forth in Section 6.10.2(a).

"***Fully Absorbed Cost of Goods***" means the costs incurred by Ionis as determined using the methodology set forth in SCHEDULE 4.9.2(c) fairly applied and as employed on a consistent basis throughout Ionis' operations.

"***Generic Product***" means, with respect to a particular Collaboration Product, one or more Third Party product(s) (i) having the same active pharmaceutical ingredient as such Collaboration Product and for which in the U.S. an ANDA has been filed naming such Collaboration Product as the reference listed drug or outside of the U.S., an equivalent process where bioequivalence to such Collaboration Product has been asserted, and (ii) such Third Party product(s) when taken in the aggregate have a market share (measured in number of prescriptions with the numerator of such fractional share being such Third Party product(s) taken in the aggregate, and the denominator being the total of such Third Party product(s) taken in the aggregate plus such Collaboration Product taken in the aggregate, as provided by IMS) during the applicable Calendar Quarter in such country of at least [***]%.

"***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.

"***High Interest Target***" has the meaning set forth in Section 1.2.3(a). For clarity, at any given time, if a gene target is not on the High Interest Target List at such time, then such gene target is not a High Interest Target.

"***High Interest Target List***" has the meaning set forth in Section 1.2.3(a).

"***HSR Act***" means the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the rules and regulations promulgated thereunder.

"***HSR Clearance***" means all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Clearance Date***" means the earliest date on which the Parties have actual knowledge that all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Filing***" means filings by Biogen and Ionis with the United States Federal Trade Commission and the Antitrust Division of the United States Department of Justice of a Notification and Report Form for Certain Mergers and Acquisitions (as that term is defined in the HSR Act) with respect to the matters set forth in this Agreement, together with all required documentary attachments thereto.

"***Incremental Tax Cost***" has the meaning set forth in Section 12.4.

"***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.

"***Indemnitee***" has the meaning set forth in Section 9.3.

"***Initial Development Plan***" has the meaning set forth in Section 1.10.2(d).

"***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 5.1.6.

"***Ionis***" has the meaning set forth in the Preamble of this Agreement.

"***Ionis Activities***" means the research, pre-clinical and/or clinical activities for which Ionis is designated as responsible under any Neurology Plan.

"***Ionis Activities Data***" has the meaning set forth in Section 1.10.2(d)(i).

"***Ionis Attribution Language***" has the meaning set forth in Section 11.4.11.

"***Ionis/Biogen Additional Agreements***" means the (i) SMN Agreement, (ii) DMPK Agreement and (iii) the Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated December 10, 2012, in each case, as amended and/or restated from time to time.

"***Ionis Breach Event***" has the meaning set forth in Section 10.4.5(a).

"***Ionis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Ionis Product-Specific Patents or Ionis Manufacturing and Analytical Patents. A list of Ionis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(a) attached hereto.

"***Ionis In-License Agreements***" has the meaning set forth in Section 6.13.1(a).

"***Ionis Internal ASO Safety Database***" has the meaning set forth in Section 5.2.7.

"***Ionis Know-How***" means any Know-How, including any Jointly-Owned Program Know-How and Ionis Program Know-How, owned, used, developed by, or licensed to Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. Ionis Know-How does not include the Ionis Manufacturing and Analytical Know-How.

"***Ionis 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 Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. Ionis Manufacturing and Analytical Know-How does not include the Ionis Know-How.

"***Ionis 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 Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Ionis Manufacturing and Analytical Patents as they related to ASOs as of the Effective Date is set forth on SCHEDULE 8.2.4(b) attached hereto. Ionis Manufacturing and Analytical Patents do not include the Ionis Product-Specific Patents or the Ionis Core Technology Patents.

"***Ionis Multi-Indication Compound***" has the meaning set forth in APPENDIX 3.

"***Ionis Neurology Target***" means a Neurology Target that (1) is not (i) a High Interest Target for which target validating activities are planned under the then-current Neurological Disease Research Plan, (ii) an ALS Target, (iii) a Collaboration Target, or (iv) a Biogen Alternate Modality Target and (2) has a Neurological Disease as its primary disease association.

"***Ionis Non-Exclusive Product***" has the meaning set forth in Section 2.1.1(c).

"***Ionis Platform Technology***" has the meaning set forth in Section 8.2.4.

"***Ionis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Ionis Product-Specific Patents as of the Effective Date is set forth on SCHEDULE 8.2.4(c) attached hereto.

"***Ionis Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Ionis Program Patents***" has the meaning set forth in Section 7.1.2.

"***Ionis Program Technology***" has the meaning set forth in Section 7.1.2.

"***Ionis Results***" has the meaning set forth in Section 4.9.3.

"***Ionis Supported Pass-Through Costs***" means [***].

"***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.

"***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.

"***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 Ionis Manufacturing and Analytical Know-How, and Ionis Know-How. For clarity, Licensed Know-How does not include any Know-How covering formulation technology or delivery devices.

"***Licensed Patents***" means the Ionis Product-Specific Patents, Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents and Ionis' 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. For clarity, Licensed Patents that are jointly-owned by Ionis and Biogen will count toward the calculation of the Full Royalty Period in a particular country if the use or sale of a Product by an unauthorized Third Party in such country would infringe a Valid Claim of such Licensed Patent.

"***Licensed Technology***" means, on a Product-by-Product basis, any and all Licensed Patents, Licensed Know-How, and any trademarks described in Section 4.1.6, to the extent necessary or useful to Develop, register, Manufacture or Commercialize such Product. Licensed Technology does not include any technology in-licensed by Ionis from [***] under the [***].

"***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 or other European Regulatory Authority after completion of Clinical Studies 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 or other country in Europe.

"***MAA Approval***" means, with respect to a particular Product, the Approval of an MAA by the EMA for such Product in any European Union country or other country in Europe.

"***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 the bulk active pharmaceutical ingredient for a Biogen Alternate Modality Product, or a Collaboration Product or Biogen Alternate Modality Product in finished form.

"***Manufacturing Process Development Terms***" means Section 4.1.3(b), Section 4.4.1(a), Section 4.4.2, Section 4.5, Section 4.6, Section 4.8.2 and Section 4.9.3 of this Agreement.

"***Measurement Period***" has the meaning set forth in Section 1.14.1(c) or Section 1.14.1(d), as applicable.

"***Milestone Event***" means a Biogen Alternate Modality Milestone Event, a Pre-Licensing Milestone Event or a Post-Licensing Milestone Event, as the case may be.

"***Minimum Third Party Payments***" means [***].

"[***]" means a disease that has, as its [***].

"***Multi-Indication Product***" means a product for a Non-Neurological Indication associated with a Multi-Indication Target.

"***Multi-Indication Target***" has the meaning set forth in Section 1.2.3(b).

"***Multi-Indication Target Notice***" has the meaning set forth in Section 1.2.3(b).

"***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 2.2.2.

"***Net Sales***" means the gross amount billed or invoiced on sales of a Product by Biogen, its Affiliates and Sublicensees, less the following: (a) customary trade, quantity, or cash discounts to non-affiliated brokers or agents to the extent actually allowed and taken; (b) amounts repaid or credited by reason of rejection or return; (c) to the extent separately stated on purchase orders, invoices, or other documents of sale, any taxes or other governmental charges levied on the production, sale, transportation, delivery, or use of such Product which is paid by or on behalf of Biogen; and (d) outbound transportation costs prepaid or allowed and costs of insurance in transit.

In any transfers of a Product between Biogen, its Affiliates and Sublicensees, Net Sales are calculated based on the final sale of such Product to an independent Third Party. If Biogen, 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. If Biogen, its Affiliates or Sublicensees uses or disposes of a Product in the provision of a commercial service, the Product is sold and the Net Sales are calculated based on the sales price of the Product to an independent Third Party during the same royalty period or, in the absence of sales, on the fair market value of the Product as determined by the Parties in good faith. Net Sales will not include any transfers of supplies of the applicable Product for (i) use in clinical trials, Pre-Clinical Studies or other research or development activities, or (ii) a *bona fide* charitable purpose; or (iii) a commercially reasonable sampling program.

With respect to Net Sales as it applies to royalties payable by Ionis, the Parties agree that any reasonable definition of "net sales" that is (x) customarily used in pharmaceutical industry technology licensing or collaboration contracts and (y) consistent with generally accepted accounting principles in the United States ("***GAAP***") or International Financial Reporting Standards and is subsequently agreed to by Ionis (or a Third Party acquirer or assignee) and Ionis' Sublicensee or commercialization partner in an arms-length transaction under a particular sublicense or commercialization agreement will replace the definition of Net Sales in this Agreement and will be used in calculating the royalty payment to Biogen on sales of products sold pursuant to such agreement. If Ionis uses such an alternate definition of "net sales" in a particular sublicense, (A) Ionis will include such "net sales" definition in the applicable royalty reports to assist Biogen with verifying royalty payments and (B) if such definition is not consistent with GAAP or International Financial Reporting Standards, upon Biogen's request, Ionis will reconcile the royalties calculated under such definition with GAAP or International Financial Reporting Standards.

"***Neurological Disease Research Plan***" has the meaning set forth in Section 1.2.

"***Neurological Disease Research Program***" has the meaning set forth in Section 1.2.

"***Neurology JDC***" has the meaning set forth in Section 1.18.3.

"***Neurology JRC***" has the meaning set forth in Section 1.18.2.

"***Neurology Plan***" means any of the following plans: (i) the Core Research Plan, (ii) the Neurological Disease Research Plan, (iii) any ASO Development Candidate Identification Plans, or (iv) any Initial Development Plans.

"***Neurology Target***" means any gene target that (i) as of the Effective Date, (y) has not been encumbered by Ionis under an agreement with a Third Party that would prevent Ionis from granting Biogen the license under Section 4.1.1 of this Agreement with respect to such gene target, and (z) has not yet achieved Target Sanction status, and (ii) as of the Effective Date or during the Research Term, the expression or activity of the gene in neurons is demonstrated to have an association to any one of the following (each of (a) through (e) below, a "***Neurological Disease***"):

[***].

For purposes of clarity, [***] are expressly excluded from the above-listed [***] and therefore any gene target that has as its primary disease association an association to [***] will not be a Neurology Target, and any [***] will not be a Product under this Agreement. In addition, [***] or [***] are expressly excluded from the above-listed [***] and therefore any gene target that has as its [***] will not be a Neurology Target. For purposes of further clarity, a gene target that has as its [***] would not be considered a Neurology Target.

"***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.

"***Non-Neurological Indications***" means therapeutic uses that are not designed to treat neurological diseases or [***] diseases.

"[***]" means diseases that have, as their [***]

"***Option***" has the meaning set forth in Section 3.1.3.

"***Option Acceleration Deadline***" has the meaning set forth in Section 1.10.2(g).

"***Option Acceleration Notice***" has the meaning set forth in Section 1.10.2(g).

"Option Deadline" means the Standard Option Deadline, the ALS Option Deadline or the Biogen Conducted Non-ALS Option Deadline, as applicable.

"***Option Period***" means, with respect to a Collaboration Program, the period beginning on the date a Neurology Target is designated a Collaboration Target hereunder and ending on the expiration or earlier termination of the Option with respect to such Collaboration Program.

"***Original Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Panel Decision***" has the meaning set forth in Section 10.4.5(b).

"***Party***" or "***Parties***" means Biogen and Ionis 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 Ionis before or after the Effective Date to any Third Party under the Ionis Core Technology Patents, the Ionis Manufacturing and Analytical Patents, or the Ionis Manufacturing and Analytical Know-How (but not under the Ionis 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) Ionis does not assist such Third Party to identify, discover or make a Compound or Product; and (2) material transfer agreements with academic collaborators or non-profit institutions solely to conduct non-commercial 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.

"***Pharmacovigilance Agreement***" has the meaning set forth in Section 5.2.2.

"***Phase 1 Trial***" means the first clinical study in human beings Initiated by Ionis or Biogen under the applicable Initial Development Plan pursuant to an IND that has been filed with a Regulatory Authority in a Major Market or Canada. If Biogen exercises the Option before Ionis Initiates such a Phase 1 Trial for a given Development Candidate, then the definition of **"*Phase 1 Trial*"** means the first clinical study of the applicable Development Candidate in human beings Initiated by Biogen, its Affiliate or its Sublicensee.

"***Phase 1 Trial Design***" means, with respect to a Collaboration Program, the Phase 1 Trial design set forth in the applicable Initial Development Plan, which may be amended from time to time during the Agreement Term as mutually agreed in writing by the Parties (in consultation with the Neurology JDC).

"***Phase 2 Trial***" means, with respect to a Product, a Clinical Study that is intended to explore the feasibility, safety, dose ranging or efficacy of such Product, that is prospectively designed to generate sufficient data (if successful) to commence a Phase 3 Trial (or foreign equivalent) of such product, as further defined in 21 C.F.R. 312.21(b) or the corresponding regulation in jurisdictions other than the United States.

"***Phase 3 Trial***" means, with respect to a Product, a pivotal Clinical Study in humans performed to gain evidence with statistical significance of the efficacy of such product in a target population, and to obtain expanded evidence of safety for such product that is needed to evaluate the overall benefit-risk relationship of such product, to form the basis for approval of an NDA by a Regulatory Authority and to provide an adequate basis for physician labeling, as described in 21 C.F.R. 312.21(c), as amended from time to time, or the corresponding regulation in jurisdictions other than the United States.

"***Phase 4 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.

"***PoC Data Package***" means, with respect to a Collaboration Product, [***], (iv) copies of all filings submitted to Regulatory Authorities regarding such Collaboration Product, (v) a summary of the patent status relating to such Collaboration Product, and (vi) a summary of any Third Party Obligations Ionis believes relate to the Collaboration Product.

"***PoC Trial***" means, with respect to a Collaboration Program, the first phase 2a Clinical Study in human patients with a pharmacokinetic or target reduction endpoint or other therapeutic or physiological endpoint.

"***PoC Trial Completion Notice***" has the meaning set forth in Section 3.1.2.

"***PoC Trial Design***" means the PoC Trial design set forth in each Initial Development Plan, which may be amended from time to time during the Agreement Term as mutually agreed in writing by the Parties (in consultation with the Neurology JDC).

"***Post-Licensing Milestone Event***" has the meaning set forth in Section 6.7.

"***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-Existing Competitive Product***" has the meaning set forth in Section 12.5.2.

"***Pre-Existing Target***" has the meaning set forth in Section 1.2.3(c).

"***Pre-Licensing Milestone Event***" means an ALS Pre-Licensing Milestone Event or a Standard Pre-Licensing Milestone Event, as applicable.

"***Primarily Neuro Multi-Indication Target***" has the meaning set forth in APPENDIX 3.

"***Primarily Other Multi-Indication Target***" has the meaning set forth in APPENDIX 3.

"***Prior Agreements***" means the agreements listed on SCHEDULE 8.2.8 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means (i) a Biogen Alternate Modality Product, or (ii) a Collaboration Product.

"***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 Collaboration Product, or (ii) methods of using a Product as a prophylactic or therapeutic; *provided however*, Patent Rights Controlled by Ionis or any of its Affiliates that (y) include claims that are directed to subject matter applicable to ASOs or products 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 (or similarly, a non-ASO molecule that binds, mimics or otherwise affects a protein or RNA that is encoded by a Biogen Alternate Modality Target and the RNA of a gene that does not encode a Biogen Alternate Modality Target), will not be considered Product-Specific Patents, and in the case of (y) and (z), such Patent Rights will be considered Ionis 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.

"*[***]***"** means a [***].

"***Receiving Party***" has the meaning set forth in Section 11.1.

"***Reduced Royalty Period***" has the meaning set forth in Section 6.10.2(d).

"***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.

"***Regulatory Materials***" means, with respect to a Product, any regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction, and any other records required by Applicable Law to be maintained that may be necessary or useful to develop, manufacture, market, sell or otherwise commercialize such Product in any such country or jurisdiction.

"***Research***" means conducting the research activities with ASOs or Compounds as set forth in the Neurology Plans, including pre-clinical research and lead optimization, *but specifically excluding* Development and Commercialization. When used as a verb, "***Researching***" means to engage in Research.

"***Research Term***" has the meaning set forth in Section 1.2.1.

"***Results***" has the meaning set forth in Section 4.9.3.

"***Reverse Royalties***" has the meaning set forth in Section 6.12.1.

"***RMC***" means Ionis' Research Management Committee, or any successor committee.

"***ROFN Period***" has the meaning set forth in Section 2.2.

"***Royalty Quotient***" has the meaning set forth in Section 6.10.2(c).

"***Service Provider***" means the Third Party(ies) conducting the original and revised studies under the applicable Initial Development Plan.

"***Setoff Amount***" has the meaning set forth in Section 10.4.5(b).

"***Setoff Dispute***" has the meaning set forth in Section 10.4.5(b).

"***Setoff Dispute Notice***" has the meaning set forth in Section 10.4.5(b).

"***SMN Agreement***" means the Development, Option and License Agreement between the Parties dated January 3, 2012, as amended and/or restated from time to time.

"***Specific Performance Milestone Events***" has the meaning set forth in Section 5.1.4.

"[***]" means the form of the [***].

"***Standard Option Deadline***" has the meaning set forth in Section 3.1.3.

"***Standard Pre-Licensing Milestone Event***" has the meaning set forth in Section 6.4.

"***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 Biogen Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Subsequent Deal***" has the meaning set forth in Section 10.2.3(b)(i).

"***Superior Patent Right***" has the meaning set forth in Section 7.2.5(c).

"***Target Related Biogen Program Claim***" has the meaning set forth in Section 4.4.4.

"***Target Related Ionis Program Claim***" has the meaning set forth in Section 4.4.2.

"***Target Sanction***" means when the therapeutic potential of a Neurology Target has been demonstrated in pre-clinical disease models and such Neurology Target has received approval by Ionis' RMC to justify expending resources to identify a human Development Candidate, all in accordance with Ionis' standard processes.

"***Target Sanction Data Package***" means, with respect to a Neurology Target, the data package Ionis presented to its RMC to obtain approval to justify expending resources to identify a human Development Candidate, all in accordance with Ionis' standard processes; *provided* such package contains the same level of detail as the data packages Ionis currently presents to its Research Management Committee to approve Ionis' own internal gene targets.

"***Technical Failure***" has the meaning set forth in Section 1.10.1(b).

"***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 Ionis and a Third Party (including the Ionis In-License Agreements) that relate to a Product, Biogen Alternate Modality Target or a Collaboration Target, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Transition Services***" has the meaning set forth in Section 10.4.6.

"***Trial Court***" has the meaning set forth in Section 10.4.5(b).

"***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 seven years, not including in calculating such seven-year period of 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 seven 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

[***]

APPENDIX 3

Multi-Indication Target Process

Neurology Targets with Broader Therapeutic Benefit.

(a) If, pursuant to Section 1.2.3(d), the CSC is unable to agree upon whether a Multi-Indication Target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target, the Parties will engage an expert panel under Section 12.1.4 to make such determination. Such expert panel will first determine the net present value ("***NPV***") of a therapeutic targeting such Multi-Indication Target and allocate such NPV between the markets for Neurological Disease indications and for Non-Neurological Indications, where such NPV calculations and allocations will take into consideration, and risk-adjust for, the relevant market sizes, competitive landscapes, scientific rationale for each market and any other factors deemed relevant by such expert panel. Based on such NPV calculations and allocations, Multi-Indication Targets will be classified as either ***"Primarily Neuro Multi-Indication Targets"***; ***"Equal Multi-Indication Targets"*** or ***"Primarily Other Multi-Indication Targets"***, where (1) a Multi-Indication Target with [***]% or more of its NPV allocated to the market for Neurological Disease indications will be a Primarily Neuro Multi-Indication Target, (2) a Multi-Indication Target with less than [***]% but more than [***]% of its NPV allocated to the market for Neurological Disease indications will be an Equal Multi-Indication Target, and (3) a Multi-Indication Target with [***]% or less of its NPV allocated to the market for Neurological Disease indications will be Primarily Other Multi-Indication Target.

(b) **Primarily Neuro Multi-Indication Targets**. If a Multi-Indication Target is classified as a Primarily Neuro Multi-Indication Target, then within [***] days of such classification, Biogen will send Ionis a written notice either (1) electing to negotiate in good faith with Ionis a development plan and [***] (i.e., [***]) for the Non-Neurological Indications if Developed and Commercialized under this Agreement, which plan and provisions will be recommended to the CSC for approval; (2) granting Ionis and its Affiliates the right to work on their own or with a Third Party to discover, develop and commercialize an oligonucleotide against such Multi-Indication Target for primarily Non-Neurological Indications (an "***Ionis Multi-Indication Compound***"); or (3) precluding Ionis and its Affiliates from working on their own or with a Third Party to discover, develop commercialize an Ionis Multi-Indication Compound. If under this clause (b) Ionis or any of its Affiliates or licensees Commercializes a product incorporating an Ionis Multi-Indication Compound, and Biogen has paid the applicable license fee under Section 6.6 for the applicable Collaboration Program, then until the earlier of (i) the [***] anniversary of the date of First Commercial Sale of such product or (ii) the date Biogen, its Affiliates and Sublicensees stop Commercializing the Product related to such Multi-Indication Target, Ionis will pay Biogen a royalty of [***]% of Annual worldwide Net Sales of such product sold by Ionis, its Affiliates or Sublicensees. The definition of Net Sales in Appendix 1 and the other provisions contained in Sections 6.14, 6.15, 6.16, and 6.17 governing payment of royalties from Biogen to Ionis will govern the payment of such royalty from Ionis to Biogen under this clause (b), *mutatis mutandis*. If within [***] days of Biogen making an election under clause (1) of this clause (b) to pursue the Non-Neurological Indication, the CSC has not agreed on a development plan and enhanced economic provisions to be paid by Biogen for the Non-Neurological Indication, then (I) Ionis and its Affiliates will not work on their own or with a Third Party to discover, develop and commercialize in the Field an Ionis Multi-Indication Compound unless otherwise permitted under this Agreement and (II) Biogen and its Affiliates will not work on their own or with a Third Party to discover, develop or commercialize Compounds related to such Multi-Indication Target for Non-Neurological Indications.

(c) **Equal Multi-Indication Targets**. If a Multi-Indication Target is classified as an Equal Multi-Indication Target, neither Party nor its respective Affiliates, licensees or Sublicensees may develop or commercialize a product targeting such Multi-Indication Target for any indication unless and until Ionis and Biogen have agreed on (i) a development plan and enhanced economic provisions to be paid by Biogen (i.e., multi-indication filing and approval milestone payments, but not additional license fees) for the Non-Neurological Indications, and (ii) the restrictions under which Ionis or Biogen (as applicable) would develop or commercialize a product targeting such Multi-Indication Target (which terms may include the requirements set forth under clause (d)(2) below).

(d) **Primarily Other Multi-Indication Targets**. If a Multi-Indication Target is classified as a Primarily Other Multi-Indication Target, then (A) Biogen may continue to Develop and Commercialize Products for Neurological Disease indications pursuant to the terms of this Agreement, and (B) within [***] days of such classification, Biogen will send Ionis a written notice either (1) electing to negotiate in good faith with Ionis and agree on a development plan and [***] (i.e., [***]) for the Non-Neurological Indications if Developed and Commercialized under this Agreement, which plan and provisions will be recommended to the CSC for approval; or (2) granting Ionis and its Affiliates the right to work on their own or with a Third Party to discover, develop and commercialize an Ionis Multi-Indication Compound so long as such Ionis Multi-Indication Compound [***], *provided*, in addition to the foregoing provisions, if the Development Candidate targeting such Multi-Indication Target being Developed or Commercialized by Biogen, its Affiliates or Sublicensees under this Agreement is [***], Ionis cannot develop or commercialize such Ionis Multi-Indication Compound for [***].

(e) If within [***] days of Biogen making an election under clause (b)(1) of this APPENDIX 3 to pursue the Non-Neurological Indication, the CSC has not agreed on a development plan and [***] (i.e., [***]) for the Non-Neurological Indications, then Ionis and its Affiliates will have the right to work on their own or with a Third Party to discover, develop and commercialize an Ionis Multi-Indication Compound so long as such Ionis Multi-Indication Compound [***].

APPENDIX 4

Form of Side Letter

[*Date*]

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer
Fax: (760) 918-3592

Re: Establishment of Cost Estimates and Milestone Payments

Dear [*Chief Operating Officer*]:

Reference is hereby made to that certain Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between Ionis and Biogen dated _____ ___, [2017] (the "***Neurology II Agreement***"), as supplemented and/or amended to date. Any capitalized terms not defined herein will have the meaning set forth in the Neurology II Agreement.

This letter memorializes the Cost Estimates and corresponding milestone payments set forth on the exhibit attached hereto as Exhibit A for the Collaboration Program and Development Candidate specified on Exhibit A, which Cost Estimates and corresponding milestone payments have been agreed by the applicable Neurology JDC in accordance with Section 1.10.2(e) of the Neurology II Agreement. Exhibit A hereto supersedes and replaces any previously approved Cost Estimates and corresponding milestone payments for the Collaboration Program and Development Candidate set forth on Exhibit A.

Please indicate your concurrence with the accuracy of Exhibit A as agreed to by the applicable Neurology JDC by executing a copy of this letter and returning it to Biogen. This letter 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 from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

[*The remainder of this page is intentionally left blank.*]

Sincerely,

[*SVP of Corporate Development*]
Senior Vice President, Corporate Development
Biogen MA Inc.

CONFIRMED ON BEHALF OF IONIS PHARMACEUTICALS, INC.:

By: _____

Name: _____

Title: _____

Date: _____

Cc: Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Fax: (760) 268-4922

Exhibit A

Collaboration Program: _____

Development Candidate: _____

[***]

[*Date*]

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer
Fax: (760) 918-3592

Re: Establishment of Biogen-Approved Costs

Dear [*Chief Operating Officer*]:

Reference is hereby made to that certain Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between Ionis and Biogen dated _____ ___, [2017] (the "***Neurology II Agreement***"), as supplemented and/or amended to date. Any capitalized terms not defined herein will have the meaning set forth in the Neurology II Agreement.

This letter memorializes certain Biogen-Approved Costs set forth on the exhibit attached hereto as Exhibit A for the Collaboration Program and Development Candidate specified on Exhibit A, which Biogen-Approved Costs have been mutually agreed by the Parties (including, if applicable, through the applicable Neurology JDC) in accordance with Section 1.14.1 of the Neurology II Agreement.

Please indicate your concurrence with the accuracy of Exhibit A as agreed to by the Parties by executing a copy of this letter and returning it to Biogen. This letter 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 from separate computers or printers. Facsimile signatures and signatures transmitted via electronic mail in PDF format will be treated as original signatures.

[*The remainder of this page is intentionally left blank.*]

Sincerely,

[*SVP of Corporate Development*]
Senior Vice President, Corporate Development
Biogen MA Inc.

CONFIRMED ON BEHALF OF IONIS PHARMACEUTICALS, INC.:

By: _____

Name: _____

Title: _____

Date: _____

Cc: Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Fax: (760) 268-4922

Exhibit A

Collaboration Program: _____

Development Candidate: _____

[***]	Biogen-Approved Costs	Apportionment of Biogen-Approved Costs under Section 1.14.1(a) [***]

SCHEDULE 1.1.4

Biogen Conducted Non-ALS Targets

1. [***]
2. [***]
3. [***]
4. [***]

SCHEDULE 1.2.3(A)

ALS Targets

1. [***]
2. [***]
3. [***]
4. [***]
5. [***]
6. [***]

SCHEDULE 1.2.4

Terms and Conditions for Provision of Research ASOs to Biogen

ARTICLE 1
DEFINITIONS

The terms used in this SCHEDULE 1.2.4 with initial letters capitalized, whether used in the singular or the plural, will have the meaning set forth in ATTACHMENT 1, or if not listed in ATTACHMENT 1, the meaning designated in places throughout the Agreement (or APPENDIX 1 to the Agreement).

ARTICLE 2
PROVISION OF RESEARCH ASOS OUTSIDE OF THE DISEASE RESEARCH PROGRAM

2.1. Scope of Collaboration.

a) Ionis will generate Research ASOs for Accepted Gene Targets in accordance with the terms and conditions of this SCHEDULE 1.2.4.

b) Each Party will devote commercially reasonable efforts to performing its obligations under the Target Validation Plan.

ARTICLE 3
CONDUCT OF THE TARGET VALIDATION OUTSIDE OF THE DISEASE RESEARCH PROGRAM

3.1. Selection of Biogen TV Targets; Target Validation Activities.

a) During the Research Term, Biogen will have the right to propose gene targets that are the focus of Biogen programs that are not part of the Collaboration (each, a "***Biogen TV Target***") for up to a total of [***] Accepted Gene Targets per [***] period. Biogen will propose such Biogen TV Targets by written notice to the Ionis Alliance Manager.

b) Ionis may reject a proposed Biogen TV Target if, at the time of such proposal, [***].

c) Each Biogen TV Target that is not rejected by Ionis will be an "***Accepted Gene Target.***" During the Research Term, Ionis and Biogen will use Commercially Reasonable Efforts to perform the activities outlined in the Target Validation Plan on each Accepted Gene Target.

3.2. Biogen's Use of Research ASOs and Information.

a) The Research ASOs and any related Confidential Information provided to Biogen by Ionis hereunder are proprietary to Ionis. Biogen will not distribute or release the Research ASOs to any Person other than its employees, academic collaborators, Affiliates, agents or (sub)contractors, solely for purposes of performing work in support of Biogen's drug discovery activities. Subject to the terms and conditions of this SCHEDULE 1.2.4, Ionis hereby grants Biogen a non-exclusive, fully paid, license to use the Ionis Confidential Information (including data generated by Ionis with Research ASOs in the performance of the Target Validation Plan) and Research ASOs solely for use in support of Biogen' drug discovery purposes. In exercising its rights under this SCHEDULE 1.2.4, Biogen may use data generated by Biogen using the Research ASOs (the "***Biogen Data***") to support Patent Rights filed by or on behalf of Biogen, including Patent Rights that claim methods of treating disease by modulating the applicable Accepted Gene Target. The claims of any such Biogen Patent Right using such Biogen Data that generically claims methods of treating disease by modulating the applicable Accepted Gene Target, but are not directed to specific compounds or agents, are referred to as the "***Biogen Licensed Claims***." Notwithstanding the foregoing, Biogen will not use such Biogen Data to support claims directed to one or more oligonucleotides as a composition of matter or one or more oligonucleotides as a pharmaceutical product, without the prior written consent of Ionis. In addition, Biogen may not use Ionis data disclosed to Biogen in connection with this SCHEDULE 1.2.4 or the Research ASOs to make products that incorporate oligonucleotides.

b) Biogen hereby grants Ionis a non-exclusive, fully-paid sublicensable license under any Biogen Licensed Claims solely for the purpose of discovering, developing or commercializing an oligonucleotide(s) as a pharmaceutical product, *provided*, *however*, that such license will only be sublicensable by Ionis to a Third Party licensee in connection with the grant of an exclusive license to such Third Party under other Ionis intellectual property with respect to such oligonucleotide. No other license is granted to Ionis under any Biogen-owned or controlled Patent Right or other intellectual property under this SCHEDULE 1.2.4. For avoidance of doubt, no rights are granted by Biogen to Ionis under this SCHEDULE 1.2.4 (expressly or by implication or otherwise) with respect to any compounds, materials or agents (or any method of use or manufacture thereof).

c) Ionis hereby grants Biogen a non-exclusive, fully-paid sublicensable license under any Ionis Licensed Claims solely for the purpose of discovering, developing or commercializing a non-oligonucleotide compound(s) as a pharmaceutical product, *provided*, *however*, that such license will only be sublicensable by Biogen to a Third Party licensee in connection with the grant of an exclusive license to such Third Party under other Biogen intellectual property with respect to any such non-oligonucleotide compound. "***Ionis Licensed Claims***" means the claims of any Ionis Invention that generically claims methods of treating disease by modulating an Accepted Gene Target, but are not directed to any specific compound or agent (including any oligonucleotide). Except as set forth in Section 3.2(a) and (c), no other license is granted to Biogen under any Ionis-owned or controlled Patent Right or other intellectual property under this SCHEDULE 1.2.4.

3.3. Non-exclusive Collaboration.

a) Ionis will perform target validation activities and will provide Research ASOs to Biogen as set forth in the Target Validation Plan on a non-exclusive basis. Ionis may collaborate with Third Parties for target validation studies on any gene targets, including Accepted Gene Targets. In addition, this SCHEDULE 1.2.4 will not limit Ionis from conducting research, discovery and development work on any and all oligonucleotides, for itself or with or on behalf of a Third Party.

b) If an oligonucleotide to an Accepted Gene Target hereunder becomes a drug development candidate of Ionis or a Third Party collaborator of Ionis, Ionis will notify Biogen. Upon receipt of such notice from Ionis, Biogen will return to Ionis all unused quantities of applicable TV Compound within [***] days after the date on which Biogen received such notice. After such time, Ionis will not have any obligation to provide additional quantities of the originally supplied TV Compound to Biogen under this SCHEDULE 1.2.4.

c) If Ionis achieves Target Sanction for an Accepted Gene Target, and Ionis does not at such time have any obligations to any Third Party with respect to such Accepted Gene Target that would conflict with Ionis' compliance with this Section 3.3(c), Ionis will provide to Biogen a Target Sanction Data Package for such Accepted Gene Target (an "***AGT Target Sanction Data Package***") and Biogen will have [***] days following receipt of such AGT Target Sanction Data Package to decide whether to negotiate with Ionis regarding an agreement with respect to such Accepted Gene Target (an "***AGT Agreement***"). Following delivery of an AGT Target Sanction Data Package, Ionis will not initiate negotiations regarding or enter into an AGT Agreement with any Third Party until the earlier to occur of: (1) Biogen notifying Ionis that it declines the opportunity to negotiate with Ionis regarding such AGT Agreement; (2) Biogen not responding to Ionis within 30 days after receipt of such AGT Target Sanction Data Package; or (3) the AGT Negotiation Period expiring before Biogen and Ionis have entered into such AGT Agreement. If Biogen or one of its Affiliates responds within [***] days after its receipt of the AGT Target Sanction Data Package indicating that Biogen or one of its Affiliates desires to negotiate with Ionis regarding the proposed AGT Agreement, Ionis and Biogen or one of its Affiliates will negotiate in good faith for 180 days thereafter (or such other period as mutually agreed by the Parties) (the "***AGT Negotiation Period***") regarding a mutually satisfactory AGT Agreement. During the AGT Negotiation Period, Biogen or its Affiliate will make the first written proposal to Ionis setting forth all material business and legal terms on which Biogen or its Affiliate would be willing to enter into the proposed AGT Agreement with Ionis; *provided* that neither Party will have any obligation to enter into an AGT Agreement. If the AGT Negotiation Period expires before Biogen or its Affiliate and Ionis have entered into such AGT Agreement, Ionis will have no further obligation to negotiate with Biogen or its Affiliates with respect to such AGT Agreement and Ionis will be free to negotiate and enter an agreement with a Third Party with respect to an AGT Agreement [***]; *provided, however*, that Ionis will not enter into any such AGT Agreement with any Third Party unless the terms and pricing of such AGT Agreement, [***].

3.4. Biogen Materials.

Any materials provided by Biogen to Ionis in connection with a Biogen TV Target or Accepted Gene Target, including any biological materials with respect to screening assays, including any progeny, expression products, mutants, replicates, derivatives and modifications thereof, (such materials being individually and collectively referred to as the "***Biogen Materials***") will be used by Ionis solely for purposes of performing activities in accordance with the Target Validation Plan and any remaining Biogen Materials will be returned to Biogen (or destroyed as may be requested by Biogen in writing) promptly following the end of the applicable activities under the Target Validation Plan or earlier upon request by Biogen. All information related to such Biogen Materials will be Biogen Confidential Information. All such materials must be used with prudence and appropriate caution in any experimental work, since all of their characteristics may not be known.

ARTICLE 4
INTELLECTUAL PROPERTY

4.1. Ownership of Inventions.

a) Title to any inventions, technology, discoveries, or other proprietary property made or discovered (as determined by the U.S. laws of inventorship) by employees of or consultants or contractors of a Party pursuant to the performance Target Validation Plan (collectively, "***Inventions***") are retained by the Party that is the employer of the inventor (or, in the case of consultants or contractors, the Party for which such consultant or contractor is providing services). Ionis will own Inventions invented solely by employees or consultants or contractors of Ionis and any Patent Rights claiming such Invention (collectively, the "***Ionis Inventions***"). Biogen will own Inventions invented solely by employees or consultants or contractors of Biogen and any Patent Rights claiming such Invention.

b) Except as provided otherwise herein, Ionis and Biogen will jointly hold title to all Inventions, made or discovered (as determined by the U.S. laws of inventorship) jointly by employees or consultants or contractors of Ionis and Biogen ("***Joint Inventions***"). Patent Rights claiming such Joint Inventions will be "***Joint Patents.***" Ionis and Biogen will promptly provide each other with notice whenever a Joint Invention is made or discovered.

c) The Parties agree, upon reasonable request, to execute any documents reasonably necessary to effect and perfect each other's ownership of any Invention or Patent Right claiming such Invention.

4.2. Patent Prosecution; Infringement of Joint Patents.

a) Each Party has the right to file, prosecute, maintain, enforce and defend Patent Rights on Inventions owned by such Party, at its own expense.

b) Ionis and Biogen will mutually agree on the filing, prosecution and maintenance of any Joint Patents and the expenses of such prosecution and maintenance will be shared equally. If either Party elects not to participate in the filing, prosecution or maintenance of a Joint Patent, it will notify the other Party of such election not later than [***] days before the applicable deadline for filing, prosecution or maintenance, and the other Party will thereafter have the right to undertake such filing, prosecution or maintenance, at its own expense.

c) A Party whose rights in a Joint Patent are impacted by the infringement of such Joint Patent by a Third Party will have the right to enforce that Joint Patent at its own discretion and at its own expense. The non-enforcing Party agrees to provide the enforcing Party all reasonable assistance (including joining such action as a Party plaintiff), at the enforcing Party's expense. Any damages or other recovery, whether by settlement or otherwise, from an action hereunder to enforce a Joint Patent will be paid first to each Party to reimburse the costs of enforcement and then prorated to the Party(ies) based on damages incurred.

ARTICLE 5
TERM AND TERMINATION

5.1. Agreement Term.

Unless the Agreement is earlier terminated (in which case this SCHEDULE 1.2.4 will also terminate), this SCHEDULE 1.2.4 will remain in effect until the end of the Research Term (the "***Term***"), at which time it will expire.

5.2. Survival.

Section 3.2 (Biogen's Use of Research ASOs and Information), Section 5.2 (Survival) and ARTICLE 4 (Intellectual Property) will survive the expiration or termination of this SCHEDULE 1.2.4.

ATTACHMENT 1 to SCHEDULE 1.2.4

Definitions

"***Accepted Gene Target***" has the meaning set forth in Section 3.1(c).

"***AGT Agreement***" has the meaning set forth in Section 3.3(c).

"***AGT Negotiation Period***" has the meaning set forth in Section 3.3(c).

"***AGT Target Sanction Data Package***" has the meaning set forth in Section 3.3(c).

"***Biogen Data***" has the meaning set forth in Section 3.2(a).

"***Biogen Licensed Claims***" has the meaning set forth in Section 3.2(a).

"***Biogen Materials***" has the meaning set forth in Section 3.4.

"***Biogen TV Target***" has the meaning set forth in Section 3.1(a).

"***Inventions***" has the meaning set forth in Section 4.1(a).

"***Ionis Inventions***" has the meaning set forth in Section 4.1(a).

"***Ionis Licensed Claims***" has the meaning set forth in Section 3.2(c).

"***Joint Invention***" has the meaning set forth in Section 4.1(b).

"***Joint Patents***" has the meaning set forth in Section 4.1(b).

"***Target Validation Plan***" means the collaborative Target Validation Plan undertaken by the Parties pursuant to this SCHEDULE 1.2.4, as further described in ATTACHMENT 2.

"***Term***" has the meaning set forth in Section 5.1.

"***TV Compound***" means an oligonucleotide delivered to Biogen by Ionis under this SCHEDULE 1.2.4 directed to an Accepted Gene Target.

ATTACHMENT 2 to SCHEDULE 1.2.4

Target Validation Plan

[***]

SCHEDULE 1.6.1

ALS Letter Agreement

[***]

SCHEDULE 1.10.2(c)

Ionis' Standard IND-Enabling Toxicology Studies

[***]

SCHEDULE 1.10.2(d)

Initial Development Plan Requirements

[***]

SCHEDULE 1.10.2(d)(v)

Study Synopsis Requirements

[***]

SCHEDULE 1.10.2(e)

Apportionment of Certain Milestone Payments and Biogen-Approved Costs

In the event that either (I) a milestone payment established under Section 1.10.2(e) or (II) Biogen-Approved Costs resulting from [***], such milestone payment or Biogen-Approved Costs, as applicable, shall be apportioned into smaller milestone payments and paid by Biogen to Ionis as follows:

[***].

Each payment due under this SCHEDULE 1.10.2(e) shall be payable by Biogen within [***] days after receipt of the applicable invoice by Biogen following the event that triggered such milestone payment.

SCHEDULE 1.10.6

Ionis API Supply for ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs

[***]

SCHEDULE 1.18.1

Collaboration Steering Committee Governance

CSC Representatives

Ionis

Lynne Parshall, Chief Operating Officer

Frank Bennett, SVP, Head of Research

Richard Geary, SVP, Head of Development

Biogen

Michael Ehlers, EVP, Research & Development

Gilmore O'Neill, SVP, Late Stage Development

John McDonald, VP Business Development

SCHEDULE 1.18.2

Neurology JRC Governance

(a) The Neurology JRC will determine the Neurology JRC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The Neurology JRC will codify these operating procedures in the written minutes of the first meeting.

(b) The Neurology JRC may hold meetings in person or by audio or video conference as determined by the Neurology JRC; but at least two meetings per year will be in person (one held at Ionis' facilities, and the other held at Biogen's facilities in the U.S.). Alliance Managers will attend Neurology 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 Neurology JRC meetings, including any subject matter expert(s) with valuable knowledge of High Interest Targets or Collaboration Targets (as applicable) or the diseases associated with such targets.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that Neurology JRC meetings occur, Neurology JRC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.18.2, Section 7.1.3 and Section 12.1, as applicable.

(d) The Neurology JRC members from the same Party will collectively have one vote. The Neurology JRC will strive to make recommendations with approval of both Ionis members and Biogen members, and record such recommendations in the minutes of the applicable Neurology JRC meeting.

(e) The Neurology 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 Neurology JRC dissolves.

SCHEDULE 1.18.3

Neurology JDC Governance

(a) The Neurology JDC will determine its operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The Neurology JDC will codify these operating procedures in the written minutes of its first meeting.

(b) The Neurology JDC may hold meetings in person or by audio or video conference as determined by the Neurology JDC; but at least two meetings per year will be in person (one held at Ionis' facilities, and the other held at Biogen's facilities in the U.S.). Alliance Managers will attend Neurology JDC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend Neurology JDC meetings, including any subject matter expert(s) with valuable knowledge of the applicable or Collaboration Target or the diseases associated with such target.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that Neurology JDC meetings occur, Neurology JDC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 1.18.3, Section 7.1.3 and Section 12.1, as applicable.

(d) Neurology JDC members from the same Party will collectively have one vote. The Neurology JDC will strive to make recommendations with approval of both Ionis members and Biogen members, and record such recommendations in the minutes of the applicable Neurology JDC meeting.

(e) The Neurology JDC 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 Neurology JDC dissolves.

SCHEDULE 1.18.6

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 Collaboration;

(c) Organizing CSC, Neurology JRC and Neurology JDC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the CSC, Neurology JRC and Neurology JDC 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 CSC, Neurology JRC and Neurology JDC;

(f) Ensuring compliance in maintaining the Ionis Internal ASO Safety Database as outlined in Section 5.2;

(g) Manage and coordinate the target validation activities under SCHEDULE 1.2.4;

(h) Ensuring proper approval of publications prior to submission as required in Section 11.4;

(i) Determining an appropriate format for summaries of resource and FTE utilization, and ensuring such summarized are timely provided to the JRC as outlined in Section 1.11.

SCHEDULE 4.4.1(a)

Drug Substance Process and Formulation Development Activities

[***]

SCHEDULE 4.9.2(c)

Ionis' Fully Absorbed Cost of Goods Methodology
Cost Estimate of API Cost per Kilogram
(OOO's)

[***]

SCHEDULE 5.1.4

Biogen's Development and Commercialization Activities

[***]

SCHEDULE 5.1.6

Integrated Development Plan Content

[***]

SCHEDULE 6.10.2(e)
Royalty Calculation Examples

[***]

SCHEDULE 6.10.2(f)

Allocation of Net Sales

[***]

SCHEDULE 6.13.1

Certain Ionis In-License Agreements

(Relevant to the High Interest Targets as of the Effective Date)

[***]

SCHEDULE 8.2.4(a)

Ionis Core Technology Patents

[***]

SCHEDULE 8.2.4(b)

Ionis Manufacturing and Analytical Patents

[***]

SCHEDULE 8.2.4(c)

Ionis Product-Specific Patents

[***]

SCHEDULE 8.2.8

Prior Agreements

[***]

SCHEDULE 10.4.5(b)

Advisory Panel Regarding Setoff Disputes

[***]

SCHEDULE 10.4.6

Transition Services

[***]

SCHEDULE 12.1.2

Mediation

1. Mediation.

1.1. If a Dispute cannot be resolved pursuant to Section 12.1.1 of the Agreement (Escalation), the Parties agree to try in good faith to resolve any such Dispute by non-binding mediation administered by the American Arbitration Association (the "***AAA***") in accordance with its Commercial Mediation Procedures then in effect (the "***Procedures***"), as modified by this Section 1.1 of this SCHEDULE 12.1.2. The mediation will be conducted by a single mediator appointed by agreement of the Parties, within 15 days after either Party notifies the other Party of its intention to mediate such Dispute, or failing such agreement, appointed by the AAA in accordance with the Procedures; *provided*, that in either case the mediator will be a retired Delaware state or federal judge. Unless otherwise mutually agreed upon by the Parties, the mediation proceedings will be conducted in Dover, Delaware. The Parties agree that they will share equally the costs and expenses of the mediation; *provided*, that each Party will bear its own attorneys' fees and associated costs and expenses. The mediation conference will be held within [***] days after appointment of the mediator, and will last no more than two consecutive days unless otherwise mutually agreed upon by the Parties. Any resolution of a Dispute by mediation pursuant to this Section 1.1 of these mediation procedures will be in writing and signed by duly authorized representatives of both Parties.

1.2. If the Parties cannot resolve a Dispute in accordance with Section 1.1 of this SCHEDULE 12.1.2, then such Dispute will be resolved by the Parties in accordance with Section 12.2 of the Agreement (Governing Law; Jurisdiction; Venue; Service of Process).

SCHEDULE 12.5

TABLE A
Applicable License Fee Payments in Change of Control for Collaboration Products

[***]

SCHEDULE 12.5

TABLE B
Applicable [***] under Section 12.5.1(b) in Change of Control

[***]

Exhibit 10.17

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(B)(4), 240.24B-2

RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT

BETWEEN

IONIS PHARMACEUTICALS, INC.

AND

BIOGEN MA INC.

TABLE OF CONTENTS

RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT

This RESEARCH COLLABORATION, OPTION AND LICENSE AGREEMENT (this "***Agreement***") is entered into as of the 19th day of December 2017 (the "***Effective Date***") by and between **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Ionis***"), and **BIOGEN MA INC.**, a Massachusetts corporation, having its principal place of business at 225 Binney Street, Cambridge, MA 02142 ("***Biogen***"). Biogen and Ionis 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, Biogen and Ionis are parties to that certain Development, Option and License Agreement, as amended (the "***Original Agreement***") dated January 3, 2012;

WHEREAS, the Parties desire to build upon their Spinraza® collaboration under the Original Agreement by entering into this Agreement to support the goal of delivering more benefit to patients; and

WHEREAS, the Parties now wish to enter this Agreement pursuant to which the Parties will collaborate on a Collaboration Program to identify an [***] Development Candidate and on a Collaboration Program to identify an [***] Development Candidate, and Biogen will obtain an Option under each such Collaboration Program to obtain an exclusive license 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

1.1. **Collaboration Overview**. The intent of the collaboration under this Agreement is (i) for Ionis to perform drug discovery activities for two separate Collaboration Programs under a mutually agreed drug discovery plan with the goal of identifying an [***] Development Candidate and an [***] Development Candidate, (ii) following Development Candidate designation for each Collaboration Program, for Biogen to conduct the IND-Enabling Toxicology Studies under such Collaboration Program, and (iii) to provide Biogen with an option under each Collaboration Program to develop and ultimately commercialize Compounds and Products under such Collaboration Program, under an exclusive license from Ionis. 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. **Drug Discovery Term**. The term for the conduct of the ASO Development Candidate Identification Plan (the "***ASO Development Candidate Identification Term***") will begin on the Effective Date and will end, on a Collaboration Program-by-Collaboration Program basis, upon the earliest [***], or (iv) a date mutually agreed by the Parties. If Biogen disagrees with Ionis' determination that a Technical Failure has occurred, Section 12.1.4 will apply.

1.3. **Collaboration Management**.

1.3.1. **Joint Steering Committee**. The Parties will establish a joint steering committee (the "***JSC***") to provide advice and make recommendations on the conduct of activities under each Collaboration Program, to govern the activities under this Agreement with respect to the discovery of potential Development Candidates, the designation of Development Candidates and the conduct of preclinical research for each Development Candidate, and to facilitate information-sharing and discussion between the Parties regarding the Development of each Development Candidate [***] for such Development Candidate. The JSC will consist of up to three representatives appointed by Ionis and up to three representatives appointed by Biogen. Each Party's JSC representatives shall be chosen by such Party in its sole discretion and may be replaced by such Party in its sole discretion upon written notice to the other Party, *provided* that each JSC member will have experience and expertise appropriate for the stage of Development of the Collaboration Programs. Each Party will designate one of its 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 JSC. The co-chairs will be responsible for overseeing the activities of the JSC consistent with the responsibilities set forth below in this Section 1.3.1. SCHEDULE 1.3.1 sets forth certain JSC governance matters agreed to as of the Effective Date for the period ending upon Option exercise with respect to each Collaboration Program. The JSC will determine the JSC operating procedures at its first meeting, including the policies for participation by additional representatives or consultants invited to attend JSC meetings, and the location of meetings, which will be codified in the written minutes of the first JSC meeting. Each Party will be responsible for the costs and expenses of its own employees or consultants attending JSC meetings. Prior to Option exercise with respect to a Collaboration Program, the JSC shall meet once per Calendar Quarter, or as otherwise mutually agreed by the Parties, *provided* that Ionis and Biogen will use reasonable efforts to schedule meetings of the JSC to take place at the same location and on the same dates as meetings of the joint development and steering committees under the Ionis/Biogen Additional Agreements, to maximize the use of each Party's time, increase information sharing efficiencies and reduce the cost of additional travel, lodging and related expenses.

(a) **Role of the JSC**. Without limiting any of the foregoing, subject to Section 1.3.2, the JSC will perform the following functions, some or all of which may be addressed directly at any given JSC meeting:

(i) review and approve amendments to the ASO Development Candidate Identification Plan proposed by either Party in accordance with Section 1.4.1(d);

(ii) review the overall progress of Ionis' efforts to discover, identify and optimize potential Development Candidates for each Collaboration Program;

(iii) establish teams and committees to oversee and manage activities under each Collaboration Program up to Development Candidate designation as it deems necessary;

(iv) review the Development Candidate Data Package for each Collaboration Program and, subject to Section 1.4.2(b), designate the Development Candidate for each Collaboration Program;

(v) establish a high-level preclinical toxicology strategy for each Development Candidate under Section 1.5;

(vi) review and discuss the initial development plan set forth in the Integrated Development Plan under Section 5.1.1 for each Development Candidate until Initiation of a Phase 3 Trial;

(vii) review the overall progress of Biogen's efforts to Develop the Development Candidates for each Collaboration Program until Initiation of a Phase 3 Trial;

(viii) establish teams and committees to oversee and manage activities under the preclinical toxicology strategy for each Development Candidate as it deems necessary;

(ix) provide input to the JPC as appropriate;

(x) assist with and participate in the resolution of disputes as contemplated in Section 12.1; and

(xi) such other review and advisory responsibilities as may be assigned to the JSC by the Parties pursuant to this Agreement.

1.3.2. Decision Making.

(a) **Committee Decision Making**. Except as expressly set forth in Sections 1.4.2(b), 1.4.3 and 1.5, decisions by the JSC will be made by unanimous consent with each Party's representatives having, collectively, one vote. At any given meeting of any such committee, a quorum will be deemed to have been reached if a voting representative of each Party is present or participating in such meeting. No action taken at any meeting of any such committee will be effective unless there is a quorum at such meeting. Unless otherwise specified in this Agreement, no action will be taken with respect to a matter for which the JSC has not reached unanimous consensus.

(b) **Implementation**. Each Party will give due consideration to, and consider in good faith, the recommendations and advice of the JSC regarding the activities within the scope of its authority. Prior to Option exercise, (i) Ionis will have the final decision-making authority regarding [***], as applicable) and [***] with respect thereto and (ii) Biogen will have the final decision-making authority regarding [***], as applicable) and [***] with respect thereto. After Option exercise for a particular Collaboration Program, subject to and without limiting Section 5.1, Biogen will have sole decision-making authority regarding the Manufacture, Development and Commercialization of Products for such Collaboration Program; *provided*, *however*, that Biogen shall not increase Ionis' costs or obligations without Ionis' consent. Except as otherwise expressly stated in this Agreement, the JSC 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.

1.3.3. JSC Activities Following Option Exercise.

(a) **JSC Meetings After Option Exercise**. On a Collaboration Program-by-Collaboration Program basis, following Option exercise with respect to a Collaboration Program until the JSC is terminated in accordance with Section 1.3.3(c) below, the JSC will meet no more than [***], in accordance with each Party's scheduling obligations set forth in Section 1.3.1, solely for the purpose of information exchange and without any decision-making authority. Notwithstanding anything to the contrary in this Section 1.3.3(a), if the Parties engage in discussions regarding the Collaboration Programs in a meeting of any governing forum under any of the Ionis/Biogen Additional Agreements, where such discussions (i) are included in the agenda for such meeting or documented in the written minutes of such meeting, or (ii) otherwise address topics other than procedure and scheduling, such discussions shall be deemed to be in lieu of the JSC meeting contemplated under this Section 1.3.3(a) for the [***] period in which such discussions occurred.

(b) **Ionis' Obligation to Participate in the JSC**. Ionis' obligation to participate in the JSC will terminate, on a Collaboration Program-by-Collaboration Program basis, upon Biogen's exercise (or expiration) of the Option for each Collaboration Program. Thereafter, Ionis will have the right, but not the obligation, to participate in such meetings with respect to such Collaboration Program upon Ionis' request, until the JSC is terminated in accordance with Section 1.3.3(c) below. Notwithstanding the foregoing, Biogen's obligations to provide Ionis with information or reports with respect to a Product shall continue in accordance with Section 5.1.1.

(c) **Termination of the JSC**. The JSC and any other subcommittees or working groups established pursuant to this Agreement will terminate, solely with respect to this Agreement and not any Ionis/Biogen Additional Agreement, on a Collaboration Program-by-Collaboration Program basis upon the earlier of (i) the Initiation of a Phase 3 Trial with respect to such Collaboration Program, and (ii) the termination of such Collaboration Program.

1.3.4. **Briefing the JSC**. At each regularly scheduled meeting of the JSC prior to exercise of the Option, each Party will provide to the JSC a progress update on its activities under each Collaboration Program.

1.3.5. **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 JSC and performing the activities listed in SCHEDULE 1.3.5.

1.4. **Collaboration**.

1.4.1. **Responsibilities**.

(a) During the ASO Development Candidate Identification Term, Ionis will use its Commercially Reasonable Efforts for each Collaboration Program to conduct drug discovery activities according to the applicable ASO Development Candidate Identification Plan, in a manner consistent with its internal practices for other gene targets, to identify an [***] Development Candidate and an [***] Development Candidate under the applicable Collaboration Program as soon as practicable.

(b) Following Development Candidate designation under a Collaboration Program, Biogen will use its Commercially Reasonable Efforts to conduct IND-Enabling Toxicology Studies for such Development Candidate, in accordance with the preclinical toxicology strategy agreed to by the JSC.

(c) The Parties may determine by mutual agreement to allocate additional Research or Development activities under a Collaboration Program to Biogen prior to the applicable Option exercise. To the extent any such Research or Development activities are allocated to Biogen in accordance with the preceding sentence, Biogen will use its Commercially Reasonable Efforts to conduct such Research or Development activities in accordance with the ASO Development Candidate Identification Plan.

(d) Either Party may propose updates to the ASO Development Candidate Identification Plan and submit such proposed updates to the JSC for its review and approval.

(e) Each Party will conduct its work under each Collaboration Program in a good scientific manner, and in compliance with all applicable good laboratory practices and cGMP, and all Applicable Laws.

1.4.2. Development Candidates.

(a) **Development Candidate Data Package**. Unless otherwise mutually agreed by the Parties, Ionis' RMC shall only approve a Compound as a potential Development Candidate for a Collaboration Program if such Compound satisfies the [***] set forth in the ASO Development Candidate Identification Plan with respect to such Collaboration Program. In addition, unless otherwise mutually agreed by the Parties, each Backup Compound set forth in the Development Candidate Data Package for a Collaboration Program must satisfy the [***] set forth in the ASO Development Candidate Identification Plan with respect to such Collaboration Program. For each Collaboration Program, Ionis will provide Biogen, through the JSC, with a complete Development Candidate Data Package promptly following the date Ionis' Research Management Committee approves a Compound as a potential Development Candidate after Ionis' completion of Ionis' activities set forth in the applicable ASO Development Candidate Identification Plan. Within [***] days of receipt of a Development Candidate Data Package pursuant to this Section 1.4.2(a), Biogen or an Affiliate will notify Ionis of any omissions or deficiencies that Biogen or its Affiliate believes in good faith cause the Development Candidate Data Package to be incomplete with respect to the potential Development Candidate or any Backup Compound described therein ("***Development Candidate Data Package Deficiency Notice***"). Ionis will promptly, and in any event within [***] days of receipt of the Development Candidate Data Package Deficiency Notice, resubmit a complete Development Candidate Data Package to Biogen or its designated Affiliate, including any information that Biogen identified in the Development Candidate Data Package Deficiency Notice. If the Parties do not agree as to whether the Development Candidate Data Package is complete, the matter will be referred to the Executives for resolution. The Executives will meet promptly and negotiate in good faith to resolve the dispute and agree upon a complete Development Candidate Data Package.

(b) **Development Candidate Designation**. Within [***] days following Ionis' delivery of a Development Candidate Data Package with respect to a Collaboration Program to Biogen pursuant to Section 1.4.2(a) (and resolution of any dispute regarding omissions or deficiencies with respect to such Development Candidate Data Package in accordance with Section 1.4.2(a)), the JSC will discuss whether to designate the Compound that is recommended by Ionis' RMC as the lead compound under such Development Candidate Data Package (or any other Compound listed in the Development Candidate Data Package as a potential backup Compound (such Compound, a "***Backup Compound***")) as the Development Candidate for such Collaboration Program, taking into account the input of the JPC with respect to its intellectual property assessment of such Compound(s). Any designation of a Development Candidate for a Collaboration Program by the JSC will be documented in the written minutes of the JSC. If the JSC mutually agrees to designate such a Compound as a Development Candidate then, following the JSC's agreement to a high level preclinical toxicology strategy for such Development Candidate in accordance with Section 1.5 below, Biogen will conduct the IND-Enabling Toxicology Studies under such strategy under Section 1.5.

If the JSC cannot agree to designate the Compound that is recommended by Ionis' RMC as the lead compound under such Development Candidate Data Package (or any Backup Compound) as a Development Candidate for a given Collaboration Program within [***] days after the JSC meets to discuss the applicable Development Candidate Data Package (such [***]-day period, the "***JSC Decision Period***"), then [***] will have final decision-making authority to determine whether or not to designate the Compound that is recommended by Ionis' RMC as the lead compound under such Development Candidate Data Package (or any Backup Compound) as a Development Candidate for such Collaboration Program and will notify the JSC in writing of [***] determination within [***] days after the end of the JSC Decision Period.

If the JSC (or [***] through the exercise of its final decision-making authority) does not designate such a Compound as a Development Candidate for a given Collaboration Program within [***] days after the date Biogen receives the complete Development Candidate Data Package under Section 1.4.2(a), then, *unless* the Parties mutually agree to amend the applicable ASO Development Candidate Identification Plan to conduct additional Development activities (i) Biogen's Option with respect to such Collaboration Program will terminate, (ii) neither Ionis nor Biogen will have an obligation to perform any further activities under this ARTICLE 1 with respect to such Collaboration Program; (iii) such program will no longer be a Collaboration Program; (iv) Ionis' obligations and Biogen's rights under this Agreement with respect to any ASOs under such Collaboration Program will then terminate except as expressly set forth in Section 1.10 and ARTICLE 2; (iv) upon Ionis' request, Biogen will provide to Ionis any data generated under the Collaboration Program and licensed to Ionis under Section 4.3.2; and (v) upon Biogen's request, Ionis will provide to Biogen any data generated under the Collaboration Program and licensed to Biogen under Section 4.3.1.

1.4.3. **Backup Development Candidates**. If, after the JSC (or [***] through the exercise of its final decision-making authority) designates a Compound as a Development Candidate for a given Collaboration Program under Section 1.4.2(b), Biogen determines that any further research, development, manufacture or commercialization of such Compound is no longer commercially reasonable or technically feasible under the then-current state of the art, then Biogen shall so notify the JSC and the JSC may designate a Backup Compound (or any other Compound) as the Development Candidate under such Collaboration Program. In the case of any dispute at the JSC regarding which Backup Compound (or other Compound), if any, to designate as the Development Candidate under such Collaboration Program, if such dispute has not been resolved within [***] days of such notice by Biogen to the JSC (or such longer period as may be mutually agreed by the Parties), such dispute shall be subject to [***] final decision-making authority as set forth in Section 1.4.2(b). Thereafter, the JSC shall promptly update the high level preclinical toxicology strategy for such Development Candidate in accordance with Section 1.5.

1.5. **IND-Enabling Toxicology Studies**. For each Collaboration Program, the JSC will agree upon a high level preclinical toxicology strategy (including the contract research organization (CRO) to be used to conduct the IND-Enabling Toxicology Studies) for each Development Candidate no later than [***] days following designation of the Development Candidate under such Collaboration Program. In addition, the JSC will approve any study protocols for the IND-Enabling Toxicology Studies at least [***] prior to the anticipated commencement of such IND-Enabling Toxicology Studies. If the JSC does not agree on such high level preclinical toxicology strategy or study protocols for a particular Collaboration Program within the applicable time period as set forth above in this Section 1.5, then Biogen will have final decision-making authority with respect thereto; *provided*, that, solely with respect to the categories of IND-Enabling Toxicology Studies listed on SCHEDULE 1.5, Biogen will not use a [***] to conduct any such IND-Enabling Toxicology Study that is not [***] listed on SCHEDULE 1.5 with respect to the applicable category of IND-Enabling Toxicology Studies, [***]

1.6. **Development Costs and Expenses**.

1.6.1. **Development Costs Paid by Ionis**. On a Collaboration Program-by-Collaboration Program basis, prior to Option exercise with respect to the applicable Collaboration Program, Ionis will be responsible for all its Research and Development activities for each Development Candidate under the applicable Collaboration Program as set forth in the applicable ASO Development Candidate Identification Plan and, except as otherwise provided under Section 1.6.2 or Section 1.8, all its costs and expenses associated therewith. For clarity, Ionis shall not have the right to use, in any such activities, any resources or funding provided to Ionis by Biogen under the Ionis/Biogen Additional Agreements.

1.6.2. **Development Costs Paid by Biogen**. On a Collaboration Program-by-Collaboration Program basis, (i) prior to Option exercise with respect to the applicable Collaboration Program, Biogen will be responsible for all its Research and Development activities for each Development Candidate under the applicable Collaboration Program in accordance with the preclinical toxicology strategy for such Collaboration Program, and all its costs and expenses associated therewith, and (ii) after Option exercise with respect to the applicable Collaboration Program, Biogen will be solely responsible for the costs and expenses related to the Development, Manufacture and Commercialization of Products, including any work performed by Ionis at Biogen's written request, and all supply chain planning and decision making.

1.7. **Manufacturing and Supply**.

Before Option exercise with respect to a Collaboration Program, (a) Ionis, [***] to support the Research and Development activities under each Collaboration Program as set forth in the applicable ASO Development Candidate Identification Plan, and (b) Biogen, [***], will be responsible for supplying the IND-Enabling Toxicology Studies pursuant to the applicable high-level preclinical toxicology strategy, *provided* that, if the Parties mutually agree, (i) Ionis will supply API (on its own or through a CMO reasonably acceptable to Biogen) sufficient to support the IND-Enabling Toxicology Studies to be conducted by Biogen in accordance with such high-level preclinical toxicology strategy, and (ii) Biogen will pay Ionis [***] for such API within [***] days of Biogen's receipt of an invoice therefor from Ionis.

1.7.1. Following Option exercise with respect to a Collaboration Program, Biogen will be responsible for Clinical Supply and Commercial supplies of API and Finished Drug Product and may contract directly with CMOs with respect to such supply in accordance with Section 4.1.2(b).

1.8. **Payment Mechanics for Additional Activities Approved by Biogen**. If Biogen desires that either Ionis or a Third Party perform additional activities under this Agreement that are not otherwise required hereunder ("***Other Activities***"), Biogen will pay the costs of conducting such work, including the cost of Ionis' time incurred in performing such work at the then-applicable [***] Rate ("[***] ***Costs***"), plus any [***] incurred by Ionis in performing such work (such costs, collectively "***Biogen-Approved Costs***"). Ionis will permit Biogen to review, negotiate (with Ionis) and approve all Biogen-Approved Costs prior to conducting any Other Activities. In advance of each [***], Ionis will provide Biogen with a good faith estimate of the Biogen-Approved Costs anticipated to be incurred in such [***]. Ionis will invoice Biogen directly for any such approved Biogen-Approved Costs incurred by Ionis and Biogen will pay the invoices submitted pursuant to this Section 1.8 for such approved Biogen-Approved Costs within [***] days after receipt of the applicable invoice by Biogen. In the case where Other Activities are performed by a Third Party, the Parties will arrange for the Third Party to directly bill Biogen and for Biogen to pay such Third Party directly.

1.9. **End of ASO Development Candidate Identification Term**. At the end of the ASO Development Candidate Identification Term for a particular Collaboration Program that did not reach the Development Candidate stage, subject to Section 1.10, (i) Biogen's Option with respect to such Collaboration Program will expire, (ii) neither Ionis nor Biogen will have an obligation to perform any activities under this ARTICLE 1 with respect to such Collaboration Program; (iii) such program will no longer be a Collaboration Program; (iv) Ionis' obligations and Biogen's rights under this Agreement with respect to any ASOs under such Collaboration Program will then terminate except as expressly set forth in Section 1.10 and ARTICLE 2; (v) upon Ionis' request, Biogen will provide to Ionis any data generated under the Collaboration Program and licensed to Ionis under Section 4.3.2; and (vi) upon Biogen's request, Ionis will provide to Biogen any data generated under the Collaboration Program and licensed to Biogen under Section 4.3.1.

1.10. **Carryover Development Candidates**. If, by the end of the ASO Development Candidate Identification Term for a particular Collaboration Program, Ionis' RMC has not designated a Compound as a Development Candidate under such Collaboration Program, and at any time during the [***] period after the end of the applicable ASO Development Candidate Identification Term (the "***Carryover Period***"), Ionis' RMC designates an ASO discovered by Ionis containing (i) [***] that is designed to bind to the RNA that encodes SMN as a development candidate ready to start IND-Enabling Toxicology Studies, or (ii) [***] that is designed to bind to the RNA that encodes SMN (other than a Specified ASO Product) as a development candidate ready to start IND-Enabling Toxicology Studies (each such ASO, a "***Carryover Development Candidate***"), then Ionis will notify Biogen and will provide Biogen with the data package presented to Ionis' RMC to approve such Carryover Development Candidate. Biogen will then have [***] days from its receipt of such package to elect to enter into an amendment to this Agreement under the same terms as set forth in this Agreement (except that [***] under Section 6.1 will be due). If, within [***] days after Biogen's receipt of such notice from Ionis, Biogen provides Ionis with written notice that it accepts such offer from Ionis for such Carryover Development Candidate, the Parties will execute an amendment to this Agreement regarding such Carryover Development Candidate on such terms. Otherwise, except for the obligation to comply with the provisions of Section 2.1, Ionis will have no further obligations and Biogen will have no further rights with respect to such Carryover Development Candidate.

ARTICLE 2.
EXCLUSIVITY COVENANTS

2.1. Exclusivity.

2.1.1. Exclusivity Covenants.

(a) **The Parties' Exclusivity Covenants During the Option Period**. Each Party agrees that, except in the performance of its obligations or exercise of its rights under this Agreement or the Original Agreement, and except as set forth in Section 2.1.2 and Section 2.1.3, 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 SMN in the Field from the Effective Date through the expiration or earlier termination of the Option (the "***Option Period***") with respect to both Collaboration Programs.

(b) **Ionis' Exclusivity Covenant After the Option Period**. Except in the performance of its obligations or exercise of its rights under this Agreement or the Original Agreement, and except as set forth in Section 2.1.2 and Section 2.1.3, Ionis 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) if Biogen timely exercises either Option (or both Options) in accordance with this Agreement, discovery, research or development in the Field of an ASO that is designed to bind to the RNA that encodes SMN until [***]; and

(ii) on a country-by-country basis, commercializing in the Field an ASO that is designed to bind to the RNA that encodes SMN until [***] in accordance with this Agreement, [***].

(c) **Biogen's Exclusivity Covenants After the Option Period**. After the Option Period with respect to a Collaboration Program, except as set forth in Section 2.1.2 and Section 2.1.3, Biogen's exclusivity obligations under Section 2.1.1(a) will be extended and will continue for so long as and to the extent of [***].

2.1.2. Limitations and Exceptions to Exclusivity Covenants.

(a) Notwithstanding anything to the contrary in this Agreement, Ionis' practice of the following will not violate Section 2.1.1:

(i) any activities pursuant to the Prior Agreements as in effect on the Effective Date;

(ii) the granting of, or performance of obligations under, Permitted Licenses;

(iii) to the extent provided in the Original Agreement, Ionis' right to commercialize Spinraza® if the Original Agreement is terminated in accordance with ARTICLE 10 of the Original Agreement unless, at the time of such termination, Biogen or any of its Affiliates, Sublicensees or distributors is Developing or Commercializing a Product under this Agreement, in which case, Ionis' right to commercialize Spinraza® under the Original Agreement shall be subject to the provisions of Section 2.1.1 *so long as* Biogen or any of its Affiliates, Sublicensees or distributors is Developing or Commercializing a Product under this Agreement;

(iv) the discovery, research or development of an ASO designed to bind to the RNA that encodes SMN in the Field where such ASO is designed to (i) [***] to work primarily in the [***] (a "[***] ***ASO Product***"), (ii) be delivered [***] to work primarily [***] (a "[***] ***ASO Product***"), or (iii) use a [***] than the [***] resulting in the [***] of that [***] that encodes a [***] protein (an "[***] ***ASO Product***", and, each such [***] ASO Product, [***] ASO Product or [***] ASO Product, a "***Specified ASO Product***"); *provided*, *however*, that any such Specified ASO Product will be treated as a "*New SMA Compound*" under Section 2.3 and, for the avoidance of doubt, Ionis shall have no right to commercialize such Specified ASO Product under Section 2.1.2(a)(v) unless Ionis has complied with its obligations under Section 2.3;

(v) on a country-by-country basis, upon [***]; *provided*, *however*, that any such Specified ASO Product will be treated as a "*New SMA Compound*" under Section 2.3 and, for the avoidance of doubt, Ionis shall have no right to commercialize such Specified ASO Product under this Section 2.1.2(a)(v) unless Ionis has complied with its obligations under Section 2.3; and

(vi) the development or commercialization of a Pre-Existing Competitive Product in accordance with Section 12.5.

(b) Notwithstanding anything to the contrary in this Agreement, Biogen's practice of the following will not violate Section 2.1.1:

(i) the discovery, research or development of a Specified ASO Product; and

(ii) on a country-by-country basis, upon [***], commercialization in such country of a Specified ASO Product;

provided that, [***] (x) if such Specified ASO Product is a [***] ASO Product, solely with respect to any [***] ASO Product of Ionis, (y) if such Specified ASO Product is a [***] ASO Product, solely with respect to any [***] ASO Product of Ionis, and (z) if such Specified ASO Product is an [***] ASO Product, solely with respect to any [***] ASO Product of Ionis.

2.1.3. **Permitted Preclinical Research**. Notwithstanding anything to the contrary in this Section 2.1, Ionis and Biogen each acknowledge and agree that, during the Agreement Term, each Party may, independently or for or with any of its Affiliates or with any Third Party acting solely for the benefit of such Party or its Affiliates (such as Third Party academic collaborators and subcontractors), conduct, with respect to a product containing an ASO that is designed to bind to the RNA that encodes SMN, preclinical research, including gene function, gene expression, target validation research, and investigating inhibition of a target in therapeutic models, but excluding drug discovery or clinical development activities.

2.2. **Effect of Exclusivity on Indications**. The Compounds are designed to bind to the RNA that encodes SMN in the Field, which is known to play a role in Spinal Muscular Atrophy. Ionis and Biogen are subject to exclusivity obligations under Section 2.1; *however*, the Parties acknowledge and agree that each Party and its Affiliates (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 a gene that is *not* SMN for any indication, even if such products are designed to treat Spinal Muscular Atrophy.

2.3. **New SMA Compounds**. With respect to any New SMA Compound designated by Ionis' RMC as a development candidate ready to start IND-Enabling Toxicology Studies, which determination shall be based on criteria substantially similar to the criteria Ionis' RMC uses to designate development candidates under other similar programs, Ionis will notify Biogen of such determination and will provide Biogen with the data package presented to Ionis' RMC to approve such development candidate (a "***New SMA Compound Notice***"). If, within [***] days after Biogen's receipt of a New SMA Compound Notice, Biogen delivers written notice to Ionis of Biogen's election to enter into an amendment to this Agreement to include such New SMA Compound within the scope of this Agreement, then upon such election the Parties will enter into an amendment to this Agreement to include such New SMA Compound within the scope of this Agreement on the terms set forth in this Agreement *provided* that (a) the Parties shall mutually agree on [***] New SMA Compound ([***] New SMA Compound [***] New SMA Compound [***] New SMA Compound), (b) if the scope of work to discover such New SMA Compound is materially larger than under any of the Development Candidate Identification Plans attached to this Agreement as of the Effective Date, then Biogen [***], (c) Biogen [***] New SMA Compound, and (d) (A) if the New SMA Compound [***].

If Biogen does not provide Ionis with written notice within such [***]-day period of Biogen's election to enter into such an amendment, or provides written notice to Ionis that it does not elect to enter into such an amendment, or if the Parties fail to mutually agree on [***] within [***] days of Biogen's election with respect to any such New SMA Compound, Ionis may initiate negotiations with a Third Party regarding a license to such New SMA Compound; *provided*, *however*, that any such Third Party shall be subject to the restrictions set forth in Section 2.1.1(b)(ii) with respect to any product containing a New SMA Compound (*provided* that, with respect to any such product that is a Specified ASO Product, such restrictions shall terminate on a country-by-country basis, upon [***]; and *provided*, *further*, that Ionis will not enter into any such license with any Third Party unless the terms and pricing of such license, [***].

Notwithstanding anything to the contrary in this Section 2.3, if, with respect to any New SMA Compound that was the subject of the license previously discussed between Biogen and Ionis, after the end of such [***]-day negotiation period and prior to Ionis entering into a license with a Third Party, any [***] regarding such New SMA Compound, then Ionis will provide Biogen with an additional New SMA Compound Notice and, if Biogen or one of its Affiliates delivers written notice to Ionis within [***] days after Biogen's receipt of such New SMA Compound Notice indicating that Biogen or one of its Affiliates desires to negotiate with Ionis regarding a license to make, use or sell such New SMA Compound, Ionis and Biogen or one of its Affiliates will negotiate in good faith with each other until the [***]day following the date of the New SMA Compound Notice (or such other period as mutually agreed by the Parties) regarding a mutually satisfactory agreement with respect to such license, which may (but shall not be required to) take the form of an amendment to this Agreement and may (but shall not be required to) be on the terms set forth in this Agreement.

2.4. **Exclusivity Under Original Agreement**. Notwithstanding anything to the contrary in this Agreement or in the Original Agreement, this ARTICLE 2 supersedes and replaces ARTICLE 2 of the Original Agreement as of the Effective Date. Notwithstanding any expiration or termination of this Agreement, if the Original Agreement remains in effect at the time of such expiration or termination, the provisions of Section 2.1.1(b)(ii), Section 2.1.1(c), and the applicable provisions of Section 2.1.2 shall survive such expiration or termination on a country-by-country basis [***]in such country and the provisions of Section 2.3 shall survive such expiration or termination [***], at which time such provisions shall terminate and be of no further force or effect.

ARTICLE 3.
EXCLUSIVE OPTION

3.1. **IND-Enabling Toxicology Studies Completion Date**. On a Collaboration Program-by-Collaboration Program basis, within [***] following the date the Draft Reports from the IND-Enabling Toxicology Studies for a Collaboration Program are available to Biogen (the "***IND-Enabling Toxicology Studies Completion Date***"), Biogen will provide to Ionis or its designated Affiliate written notice thereof together with a copy of each such Draft Report.

3.2. **Option and Option Deadline**. On a Collaboration Program-by-Collaboration Program basis, Ionis hereby grants to Biogen and its Affiliates an exclusive option to obtain the license set forth in Section 4.1.1 with respect to such Collaboration Program (each, an "***Option***"). Each Option for a Collaboration Program will be available to Biogen and its Affiliates until 5:00 pm (Eastern Time) on the [***] (A) the [***] following the IND-Enabling Toxicology Studies Completion Date for the applicable Collaboration Program, and (B) the [***] anniversary of the date the Development Candidate was designated for such Collaboration Program under Section 1.4.2(b) (the "***Option Deadline***"); *provided*, *however*, if Biogen determines that an HSR Filing is required to be made under the HSR Act to exercise the Option and notifies Ionis of such determination within [***] after the IND-Enabling Toxicology Studies Completion Date, the Parties will promptly file an HSR Filing in accordance with Section 3.3 and the Option Deadline will be extended until 5:00 pm (Eastern Time) on the fifth Business Day after the HSR Clearance Date. If, by the Option Deadline, Biogen or its designated Affiliate (i) notifies Ionis in writing that it wishes to exercise the Option, and (ii) pays to Ionis the license fee set forth in Section 6.2, Ionis will, and hereby does, grant to Biogen or its designated Affiliate the license set forth in Section 4.1.1. If, by the Option Deadline, Biogen or its designated Affiliate has not both (y) provided Ionis a written notice stating that Biogen is exercising its Option, and (z) paid Ionis the license fee in accordance with Section 6.2, then Biogen's Option for the applicable Collaboration Program will expire and (a) upon Ionis' request, Biogen will provide to Ionis any data generated under the Collaboration Program and licensed to Ionis under Section 4.3.2, and (b) upon Biogen's request, Ionis will provide to Biogen any data generated under the Collaboration Program and licensed to Biogen under Section 4.3.1.

3.3. **HSR Compliance**.

3.3.1. **HSR Filing**. If Biogen notifies Ionis pursuant to Section 3.2 that an HSR Filing is required to exercise an Option under this Agreement, each of Biogen and Ionis will, within five Business Days after such notice from Biogen (or such later time as may be agreed to in writing by the Parties), file with the United States Federal Trade Commission ("***FTC***") and the Antitrust Division of the United States Department of Justice ("***DOJ***"), any HSR Filing required with respect to the transactions contemplated hereby. The Parties will cooperate with one another to the extent necessary in the preparation of any such HSR Filing. Each Party will be responsible for its own costs and expenses (other than filing fees, which Biogen will pay) associated with any HSR Filing.

3.3.2. **HSR Clearance**. In furtherance of obtaining HSR Clearance for an HSR Filing filed under Section 3.3.1, Ionis and Biogen will use their respective commercially reasonable efforts to resolve as promptly as practicable any objections that may be asserted with respect to this Agreement or the transactions contemplated by this Agreement under any antitrust, competition or trade regulatory law. In connection with obtaining such HSR Clearance from the FTC, the DOJ or any other governmental authority, Biogen and its Affiliates will not be required to (i) sell, divest (including through a license or a reversion of licensed or assigned rights), hold separate, transfer or dispose of any assets, operations, rights, product lines, businesses or interest therein of Biogen or any of its Affiliates (or consent to any of the foregoing actions); or (ii) litigate or otherwise formally oppose any determination (whether judicial or administrative in nature) by a governmental authority seeking to impose any of the restrictions referenced in clause (i) above.

3.4. Restrictions on Ionis' Right to Grant Diagnostic Rights; Right to Negotiate Diagnostic Rights.

3.4.1. Ionis hereby grants to Biogen and its Affiliates an option (the "***Diagnostic Option***") to negotiate during the Full Royalty Period the terms of an agreement under which [***]. The Diagnostic Option will be available to Biogen and its Affiliates until the expiration of the [***].

3.4.2. During the [***], Ionis (i) has the right to [***], and (ii) will not [***].

3.4.3. If, during the [***], Ionis grants any Third Party a [***], then Ionis will promptly notify Biogen of such [***] and will offer Biogen a [***].

ARTICLE 4.
LICENSE GRANTS

4.1. License Grants to Biogen.

4.1.1. Development and Commercialization License. Subject to the terms and conditions of this Agreement, on a Collaboration Program-by-Collaboration Program basis, effective upon Biogen's exercise of the Option for a particular Collaboration Program in accordance with this Agreement, Ionis grants to Biogen a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 4.1.2 below) license under the Licensed Technology to research, Develop, Manufacture, have Manufactured (in accordance with Section 4.1.2 below), register, market and Commercialize Products under such Collaboration Program in the Field.

4.1.2. Sublicense Rights; CMO Licenses.

(a) Subject to the terms and conditions of this Agreement, Biogen will have the right to grant sublicenses under the licenses granted under Section 4.1.1 above and Section 4.4.1(b) below:

(i) under the Ionis Core Technology Patents, Ionis Product-Specific Patents (to the extent not assigned under Section 4.2.1) and Ionis Know-How, to an Affiliate of Biogen or a Third Party; and

(ii) under the Ionis Manufacturing and Analytical Patents and Ionis Manufacturing and Analytical Know-How, solely to (x) [***] or (y) [***];

provided that each such sublicense will be subject to, and consistent with, the terms and conditions of this Agreement. If, within [***] days of first learning of any breach of such sublicense terms, Biogen 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 Ionis, Biogen hereby grants Ionis the right to enforce such sublicense terms on Biogen's behalf and will cooperate with Ionis (which cooperation will be at Biogen's sole expense, and will include Biogen joining any action before a court or administrative body filed by Ionis against such Sublicensee if and to the extent necessary for Ionis to have legal standing before such court or administrative body) in connection with enforcing such terms. Biogen will provide Ionis 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 Biogen's selecting and engaging one or more CMOs to supply Clinical Supplies or supply API and Finished Drug Product for Development or Commercialization, Ionis will, at Biogen's option, either (1) grant a license from Ionis [***] under the [***] to the extent necessary for [***], which Ionis agrees it will grant to [***], or (2) permit Biogen to grant a sublicense from Biogen to [***]. For the Products, each such manufacturing agreement between Biogen and a CMO will contain [***]. Biogen will provide Ionis with a true and complete copy of any manufacturing agreement entered into with a CMO within [***] days after the execution thereof. Notwithstanding the foregoing, if Ionis fails to comply with the terms of this Section 4.1.2(b) and does not cure such failure within 90 days after written notice from Biogen specifying the details of any such failure, Biogen will have the right to [***].

4.1.3. Effect of Termination on Sublicenses.

(a) If this Agreement terminates for any reason, any Sublicensee of Biogen will, from the effective date of such termination, automatically become a direct licensee of Ionis with respect to the rights sublicensed to the Sublicensee by Biogen; *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 Biogen, and (iii) such Sublicensee agrees to pay directly to Ionis such Sublicensee's payments under this Agreement to the extent applicable to the rights sublicensed to it by Biogen. Biogen agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of Ionis and if requested, the Sublicensee.

(b) If this Agreement terminates for any reason, any Sublicensee of Biogen under Section 4.4.2 and any Sublicensee of Ionis under Section 4.6.2 will, from the effective date of such termination, automatically become a direct licensee with respect to the rights sublicensed to the Sublicensee by the applicable Party hereunder; *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 such Sublicensee, and (iii) with respect to Sublicensees of Ionis, such Sublicensee agrees to pay directly to Biogen such Sublicensee's payments under Section 4.5.2 to the extent applicable to the rights sublicensed to it by Ionis. Each Party agrees that it will confirm clause (i) of the foregoing in writing at the request and for the benefit of the other Party and if requested, the Sublicensee.

4.1.4. **No Implied Licenses**. All rights in and to Licensed Technology not expressly licensed to Biogen under this Agreement are hereby retained by Ionis or its Affiliates. All rights in and to Biogen Technology not expressly licensed or assigned to Ionis under this Agreement, are hereby retained by Biogen 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.

4.1.5. **License Conditions; Limitations**. Subject to Section 6.8, 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 Ionis In-License Agreements, in each case to the extent the provisions of such obligations or agreements have been specifically disclosed to Biogen in writing (or via electronic data room) prior to Biogen's exercise of an Option. With respect to each Product, Ionis will promptly disclose to Biogen any Third Party Obligations Ionis believes apply to such Product during the Agreement Term, and Biogen 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 Ionis written notice prior to Option exercise. If, prior to Option exercise, Biogen provides Ionis with such a written notice to exclude certain Third Party Patent Rights and Know-How from such license, such Third Party Patent Rights and Know-How will not be included in the Licensed Technology licensed with respect to the applicable Product under this Agreement. If Biogen does not provide Ionis with such a written notice to exclude such Third Party Patent Rights and Know-How prior to Option exercise, such Third Party Patent Rights and Know-How (and any Third Party Obligations to the extent applicable to the applicable Product) will be included in the Licensed Technology licensed with respect to the applicable Product under this Agreement.

4.1.6. **Trademarks for Products**. Biogen or its designated Affiliate will be solely responsible for developing, selecting, searching, registering and maintaining and 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 Ionis Product-Specific Patents; Grant Back to Ionis.

4.2.1. Assignment to Biogen. Within [***] after Biogen has paid Ionis [***] under Section 6.3 and following review and consideration by the JPC, Ionis will assign to Biogen or one or more of its designated Affiliates, Ionis' ownership interest in (i) all Ionis Product-Specific Patents related to such Collaboration Program that are owned by Ionis (whether solely owned or jointly owned with one or more Third Parties), and (ii) any Jointly-Owned Program Patents Covering Products related to such Collaboration Program.

4.2.2. Grant Back to Ionis. Biogen grants to Ionis a worldwide, sublicensable license under any Ionis Product-Specific Patents and Jointly-Owned Program Patents assigned to Biogen under Section 4.2.1, which license shall be exclusive with respect to such Ionis Product-Specific Patents and non-exclusive with respect to such Jointly-Owned Program Patents, (i) for all [***], and (ii) to [***] to the extent permitted by this Agreement.

4.2.3. Original Agreement. Notwithstanding anything to the contrary in the Original Agreement, with respect to Isis Product-Specific Patents and Jointly-Owned Program Patents (each as defined in the Original Agreement) assigned to Biogen under Section 4.2.1 of the Original Agreement, Biogen shall retain (i) the non-exclusive right under such Isis Product-Specific Patents and Jointly-Owned Program Patents to the extent necessary for Biogen to conduct any Biogen Activities that are Development activities with respect to any Development Candidate during the Option Period in accordance with this Agreement, (ii) effective upon Biogen's exercise of the Option for a particular Collaboration Program in accordance with this Agreement, and without limiting the provisions of Section 6.6.1(b), the [***] and (iii) the [***] to the extent permitted by this Agreement. This Section 4.2.3 amends and supersedes Section 4.2.2 of the Original Agreement to the extent of any conflict.

4.3. Data Licenses.

4.3.1. Data License to Biogen. Ionis hereby grants Biogen a worldwide, non-exclusive, royalty-free, sublicenseable license under any data included in the Ionis Program Know-How for (a) any use other than in connection with the development, manufacture or commercialization of an Oligonucleotide and (b) use in connection with the development, manufacture or commercialization of any Oligonucleotide that is being developed or commercialized by the Parties under any Ionis/Biogen Additional Agreement.

4.3.2. Data License to Ionis. Biogen hereby grants Ionis a worldwide, non-exclusive, royalty-free, sublicenseable license under any data included in the Biogen Program Know-How solely for use in connection with the development, manufacture or commercialization of Oligonucleotides to the extent permitted by this Agreement and any Ionis/Biogen Additional Agreement.

4.4. Enabling Licenses.

4.4.1. Licenses During the Option Period.

(a) Subject to the terms and conditions of this Agreement, Ionis hereby grants Biogen a worldwide, non-exclusive, sublicensable (but only as permitted in Section 4.4.2 below), royalty-free license under the Ionis Manufacturing and Analytical Know-How and Ionis Manufacturing and Analytical Patents solely to conduct Manufacturing and drug substance process and formulation development activities with respect to any Compound or Product under any Collaboration Program during the Option Period for such Collaboration Program; *provided* that the grant of rights pursuant to this Section 4.4.1(a) shall not include the right to Manufacture any Compound or Product for Commercialization.

(b) Subject to the terms and conditions of this Agreement (including Biogen's exclusivity covenants under Section 2.1.1), solely to the extent necessary for Biogen to conduct any Biogen Activities that are Development activities with respect to any Development Candidate during the Option Period in accordance with this Agreement, Ionis hereby grants Biogen a worldwide, non-exclusive, sublicensable (but only as permitted in Section 4.1.2 above), royalty-free license under the Licensed Technology. Biogen will pay Ionis [***] within [***] days after Biogen's receipt of the applicable invoice. For clarity, the grant of rights pursuant to this Section 4.4.1(b) shall not include the right to Commercialize any such Product or to Manufacture any such Product for Commercialization.

4.4.2. Biogen's Right to Sublicense. Biogen will have the right to grant sublicenses under the license granted under Section 4.4.1(a) above (a) in the case of a sublicense of Biogen's right to conduct Manufacturing of Compounds or Products, other than any sublicense to conduct manufacturing in support of drug substance process and formulation development activities, solely to (i) [***] or (ii) a [***] and (b) in the case of a sublicense of Biogen's right to conduct drug substance process and formulation development activities, including manufacturing in support thereof, to [***], *provided* that each such sublicense will be subject to, and consistent with, the Manufacturing Process Development Terms. If, within [***] days of first learning of any breach of such sublicense terms by any such Sublicensee, Biogen fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.4.2, which failure would cause an adverse effect on Ionis, Biogen hereby grants Ionis the right to enforce such sublicense terms on Biogen's behalf and will cooperate with Ionis (which cooperation will be [***], and will include Biogen joining any action before a court or administrative body filed by Ionis against such Sublicensee if and to the extent necessary to have legal standing before such court or administrative body) in connection with enforcing such terms. Biogen will provide Ionis with a true and complete copy of any sublicense granted pursuant to this Section 4.4.2 within 30 days after the execution thereof. For the avoidance of doubt, Section 4.1.3(b) shall apply to sublicenses granted under this Section 4.4.2.

4.4.3. **Enabling License to Biogen**. Subject to the terms and conditions of this Agreement (including Biogen's exclusivity covenants under Section 2.1.1), Ionis hereby grants Biogen an irrevocable, worldwide, non-exclusive, sublicenseable license under any Ionis Program Technology Controlled by Ionis or its Affiliates at any time during the Agreement Term to research, develop, manufacture, have manufactured and commercialize (a) a product that is being developed or commercialized by Biogen, its Affiliates or its Sublicensee under any Ionis/Biogen Additional Agreement other than this Agreement, (b) products that do not include an Oligonucleotide as an active pharmaceutical ingredient, (c) Gene-Editing Products and (d) Duplex Products. Such license in clause (b), clause (c) and clause (d) above is royalty-free; *except* that if a product being sold by Biogen, its Affiliates or Sublicensees is Covered by a Target Related Ionis Program Claim, then on a country-by-country basis Biogen will pay Ionis a royalty equal to [***]% of Net Sales of any product sold by Biogen, its Affiliates or Sublicensees so long as such product is Covered by such Target Related Ionis Program Claim in such country. A "***Target Related Ionis Program Claim***" means a Valid Claim that (i) is within an Ionis Program Patent that is solely owned by Ionis, (ii) Covers a product being sold by Biogen, its Affiliates or Sublicensee, and (iii) claims a gene target, or a method of modulating such gene target to achieve a prophylactic or therapeutic effect/benefit.

4.4.4. **Enabling License to Ionis**. Subject to the terms and conditions of this Agreement (including Ionis' exclusivity covenants under Section 2.1.1), Biogen hereby grants Ionis an irrevocable, worldwide, non-exclusive, sublicenseable license under any Biogen Program Technology Controlled by Biogen or its Affiliates at any time during the Agreement Term, other than any Biogen Results licensed to Ionis under Section 4.5.1, to research, develop, manufacture, have manufactured and commercialize (a) products that include an Oligonucleotide as an active pharmaceutical ingredient (other than products that 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 under this Agreement or any other Ionis/Biogen Additional Agreement), (b) Gene-Editing Products and (c) Duplex Products. Such licenses are royalty-free; except that if a product being sold by Ionis, its Affiliates or Sublicensee is Covered by a Target Related Biogen Program Claim, then on a country-by-country basis Ionis will pay Biogen a royalty equal to [***]% of net sales of any product sold by Ionis, its Affiliates or Sublicensees, for so long as such product is Covered by such Target Related Biogen Program Claim in such country. For the purpose of the foregoing royalty calculation, "net sales" will be calculated in accordance with the definition of "Net Sales" as set forth in APPENDIX 1, applied *mutatis mutandis* to such calculation. The provisions of Sections 6.8.3(b) through 6.12 shall apply, *mutatis mutandis*, to any royalty payments by Ionis to Biogen under this Section 4.4.4. A "***Target Related Biogen Program Claim***" means a Valid Claim that (i) is within a Biogen Program Patent that is solely owned by Biogen, (ii) Covers a product being sold by Ionis, its Affiliates or Sublicensee, and (iii) claims a gene target, or a method of modulating such gene target to achieve a prophylactic or therapeutic effect/benefit.

4.5. Licenses to Ionis for Biogen Results.

4.5.1. Subject to the terms and conditions of this Agreement, Biogen hereby grants Ionis an irrevocable, worldwide, non-exclusive, sublicensable license under the Biogen Results Controlled by Biogen or its Affiliate at any time during the Agreement Term, to research, develop, make, have made, import, export, use and sell (a) products that include an Oligonucleotide as an active pharmaceutical ingredient (other than products that 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 the Parties pursuant to an Option or exclusive license granted from Ionis to Biogen under the Ionis/Biogen Additional Agreements), (b) Gene-Editing Products and (c) Duplex Products.

4.5.2. The licenses granted in Section 4.5.1 shall be royalty-free with respect to any unpatented Know-How within the Biogen Results and with respect to any Biogen Manufacturing Program Patent that Ionis or its Affiliates exploits solely in connection with Ionis' or its Affiliates' internal programs. Such licenses will be royalty-bearing with respect to any Biogen Manufacturing Program Patent, including any Biogen Manufacturing Program Patent with respect to which Biogen files a patent application at any time after such Biogen Results arose, that Ionis sublicenses to a sublicensee (other than Third Party sublicensees acting on Ionis' or its Affiliates' behalf in connection with Ionis' or its Affiliates' internal programs) as follows: on a country-by-country, product-by-product and Biogen Manufacturing Program Patent-by-Biogen Manufacturing Program Patent basis, Ionis will pay Biogen a royalty on net sales of each such product equal to (a) [***]% if the product sold by or on behalf of Ionis' Third Party sublicensees is Covered by one Biogen Manufacturing Program Patent, for so long as such product is Covered by such Biogen Manufacturing Program Patent in such country; (b) [***]% if the product sold by or on behalf of Ionis' Third Party sublicensees is Covered by two Biogen Manufacturing Program Patents, for so long as such product is Covered by such Biogen Manufacturing Program Patents in such country; (c) [***]% if the product sold by or on behalf of Ionis' Third Party sublicensees is Covered by three Biogen Manufacturing Program Patents, for so long as such product is Covered by such Biogen Manufacturing Program Patents in such country; and (d) [***]% if the product sold by or on behalf of Ionis' Third Party sublicensees is Covered by four or more Biogen Manufacturing Program Patents, for so long as such product is Covered by such Biogen Manufacturing Program Patents in such country. The foregoing royalties shall not be cumulative, and in no event shall the royalty payable by Ionis under this Section 4.5.2 exceed [***]% of net sales of any such product. If one or more Biogen Manufacturing Program Patents expires, is invalidated or otherwise ceases to Cover a product bearing royalties as set forth above, the applicable royalty rate under this Section 4.5.2 shall be recalculated to reflect the number of Biogen Manufacturing Program Patents then-Covering such product. For the purpose of the foregoing royalty calculation, "net sales" will be calculated as follows: (i) in the case where the applicable sublicense agreement contains a definition of net sales that is customarily used in pharmaceutical industry technology licensing or collaboration contracts and was negotiated in good faith at arms-length, the definition of net sales under such sublicense agreement will be used in calculating the royalty payment to Biogen under this letter agreement, or (ii) in the case where (i) does not apply, the definition of "Net Sales" as set forth in APPENDIX 1 of this Agreement will be used *mutatis mutandis*. If Ionis grants a sublicense under this Section 4.5 to an entity that is an Ionis Affiliate at the time Ionis grants such sublicense, such applicable sublicense will [***], *except* that any sublicense Ionis grants to [***] under this Section 4.5.2 will [***]. The provisions of Sections 6.8.3(b) through 6.12 shall apply, *mutatis mutandis*, to any royalty payments by Ionis to Biogen under this Section 4.5.2.

4.6. Right to Obtain Direct License from Biogen to Ionis Partner; Sublicensees of Ionis.

4.6.1. If requested by Ionis, Biogen shall grant a direct, royalty-bearing license under the Biogen Results to a *bona fide* Third Party licensee or Affiliate of Ionis designated by Ionis on the same terms as set forth in Section 4.5 with respect to sublicenses of Ionis. Biogen shall endeavor in good faith to grant such license within thirty (30) days of any such request by Ionis.

4.6.2. Ionis will have the right to grant sublicenses under the licenses granted under Section 4.5, *provided* that each such sublicense will be subject to, and consistent with, the terms and conditions of this Agreement. If, within [***] of first learning of any breach of such sublicense terms, Ionis fails to take any action to enforce the sublicense terms of a sublicense granted pursuant to this Section 4.6.2, which failure would cause an adverse effect on Biogen, Ionis hereby grants Biogen the right to enforce such sublicense terms on Ionis' behalf and will cooperate with Biogen (which cooperation will [***], and will include Ionis joining any action before a court or administrative body filed by Biogen against such Sublicensee if and to the extent necessary for Biogen to have legal standing before such court or administrative body) in connection with enforcing such terms. Ionis will provide Biogen with a true and complete copy of any sublicense granted pursuant to this Section 4.6.2 within 30 days after the execution thereof.

4.7. Ownership of and Assistance with Regulatory Filings.

4.7.1. **In General**. After exercising the Option for a particular Collaboration Program, Biogen will have sole ownership of all INDs, NDAs, MAAs, orphan drug designations and other regulatory filings and documentation with respect to the Products under such Collaboration Program. If Biogen requests, Ionis will assist Biogen in preparing regulatory filings for the Products, under terms negotiated in good faith between Ionis and Biogen, including payment for Ionis' time at Ionis' then applicable FTE Rate plus any reasonable out-of-pocket expenses incurred by Ionis in providing such assistance, utilizing the payment mechanism set forth in Section 1.8.

4.7.2. **Priority Review Vouchers**. After exercising the Option for a particular Collaboration Program, if Biogen receives a Priority Review Voucher from the FDA for the applicable Development Candidate or Product, the following provisions will apply:

(a) Biogen will be the sole and exclusive owner of such Priority Review Voucher;

(b) if Biogen [***] or [***] such Priority Review Voucher [***], then [***] such Priority Review Voucher will [***] for the applicable [***] in the [***] which [***] is [***], subject to all applicable [***]; and

(c) Biogen will determine, in its sole discretion, whether to [***] the Priority Review Voucher [***] or [***] the Priority Review Voucher [***]. If Biogen determines to [***] the Priority Review Voucher [***], then Biogen will consider in good faith [***], to the [***] the Priority Review Voucher [***] or any of the [***].

4.8. **Subcontracting**.

4.8.1. Subject to the terms of this Section 4.8, 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. Each Party will be responsible for any income or non-income taxes that arise as a result of such Party's use of any Third Party subcontractors hereunder, including payroll, income, withholding, sales and use, VAT, customs, duties excise or property taxes, and such taxes will not be reimbursable expenditures.

4.8.2. Ionis agrees that, where Biogen wishes to (sub)contract with a Third Party with respect to any of the rights granted under Section 4.4.1(a), Ionis shall, within [***] of any request by Biogen, provide Biogen with a letter of authorization as necessary for Biogen to be able to contract with such Third Party in accordance with the terms of this Agreement. Biogen will ensure that any Third Party (sub)contractors Biogen uses to conduct the process development or manufacturing activities contemplated by Section 4.4.1(a) will be obligated to assign to Biogen all right, title and interest in and to any inventions developed by such (sub)contractors in the performance of such activities. Biogen will not enter into any new agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case that restricts, limits, diminishes or encumbers the rights granted to Ionis under the Manufacturing Process Development Terms. In addition, after the Effective Date, Biogen will use reasonable efforts to include, in any agreement with a (sub)contractor that has substantial material obligations related to the Development, Manufacture or Commercialization of a Product, provisions requiring that, in the event the applicable Option is terminated, expires unexercised or this Agreement is terminated, such (sub)contractor would enter into an agreement with Ionis with respect to such Product that is substantially similar to such (sub)contractor's agreement with Biogen and would reasonably cooperate with Ionis to facilitate the transition of such Product to Ionis following such termination or Option expiration, including the transfer to Ionis of data and information in such (sub)contractor's possession related to the Product.

4.9. Technology Transfer.

4.9.1. **Technology Transfer to Biogen during the Option Period**. Within [***] after the Effective Date, Ionis will deliver to Biogen or one or more designated Affiliates, solely for use by Biogen, its Affiliates or a Third Party acting on Biogen's behalf to conduct any Biogen Activities that are Development activities and any Manufacturing activities permitted under Section 4.4.1(a) in accordance with this Agreement, all Ionis Know-How and Ionis Manufacturing and Analytical Know-How in Ionis' Control that is necessary to conduct such Biogen Activities. If requested by Biogen, Ionis will provide Biogen with a reasonable level of assistance in connection with such transfer, which Biogen will reimburse Ionis for its time incurred in providing such assistance at the then-applicable FTE Rate, plus any reasonable out-of-pocket expenses incurred by Ionis in providing such assistance, using the payment mechanism set forth in Section 1.8.

4.9.2. **Technology Transfer to Biogen after Option Exercise**. On a Collaboration Program-by-Collaboration Program basis, Ionis will promptly, but no later than [***] after Biogen exercises its Option for such Collaboration Program hereunder, deliver to Biogen or one or more designated Affiliates:

(a) **Ionis Know-How**. All Ionis Know-How in Ionis' possession that has not previously been provided hereunder, for use solely in accordance with the licenses granted under Section 4.1.1 and Section 10.4.2, and Ionis will and does hereby assign to Biogen all of Ionis' right, title and interest in and to all Regulatory Materials (including drafts) that relate to the applicable Development Candidate; *provided* that, (x) notwithstanding the foregoing, and subject to the provisions of Section 2.1, the Parties acknowledge that Ionis shall be permitted to use excerpts or portions of any such assigned Regulatory Materials in any other regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction related to products other than the Development Candidate, *provided, further* that such excerpts or portions shall not include (i) any non-public data or information, in each case, related solely to the applicable Development Candidate, or (ii) any Confidential Information of Biogen, and (y) for clarity, such assignment of Ionis' right, title and interest in and to such Regulatory Materials shall not include the assignment of any Know-How (including any data) contained therein. If Ionis intends to use any excerpt or portion of any such assigned Regulatory Materials in accordance with clause (x) of the preceding sentence that are not in the public domain and do not relate to Ionis' antisense oligonucleotide platform, Ionis shall, at least 30 days in advance of the anticipated submission of such excerpt or portion to a Regulatory Authority, notify Biogen of such intent and provide to Biogen a copy of such proposed excerpt or portion for review and comment. The Parties shall discuss in good faith any comments of Biogen with respect to such proposed excerpt or portion prior to submission thereof. To assist with the transfer and assignment of such Ionis Know-How, Ionis will make its personnel reasonably available to Biogen during normal business hours for up to [***] ([***]) of Ionis' time for each Collaboration Program to transfer such Ionis Know-How under this Section 4.9.2(a). Thereafter, if requested by Biogen, Ionis will provide Biogen with a reasonable level of assistance in connection with such transfer, which Biogen will reimburse Ionis for its time incurred in providing such assistance at the then-applicable FTE Rate, plus any reasonable out-of-pocket expenses incurred by Ionis in providing such assistance, using the payment mechanism set forth in Section 1.8.

(b) **Ionis Manufacturing and Analytical Know-How**. Solely for use by Biogen, its Affiliates or a Third Party acting on Biogen's behalf to Manufacture API in Biogen's own or an Affiliate's manufacturing facility, all Ionis Manufacturing and Analytical Know-How in Ionis' Control relating to Products, which is necessary for the exercise by Biogen, its Affiliates or a Third Party of the Manufacturing rights granted under Sections 4.1.1. Upon Biogen's request, subject to Section 4.1.2, Ionis will provide up to [***] for [***] ([***]) of its time for each Collaboration Program to transfer such Ionis Manufacturing and Analytical Know-How under this Section 4.9.2(b) to any Third Party Manufacturing API or Finished Drug Product on Biogen's behalf solely to Manufacture API or Finished Drug Product in accordance with the terms of this Agreement. Thereafter, if requested by Biogen, Ionis will provide Biogen with a reasonable level of assistance in connection with such transfer, which Biogen will reimburse Ionis for its time incurred in providing such assistance at the then-applicable FTE Rate, plus any reasonable out-of-pocket expenses incurred by Ionis in providing such assistance, using the payment mechanism set forth in Section 1.8.

(c) **API and Product**. Upon Biogen's written request, Ionis will sell to Biogen any bulk API, Clinical Supplies and Finished Drug Product, and any intermediates, impurity markers and reference standards relating to a Product in Ionis' possession at the time of the applicable Option exercise, at a price equal to [***].

4.9.3. **Results**.

(a) Each Party shall share with the other Party on an Annual basis (preferably at in-person meetings) the results of such Party's manufacturing process development activities, including all data, the identity and location of vendors, information and results received from vendors, and planned additional work, (a) in the case of Biogen, to the extent arising under the Manufacturing Process Development Terms (all Know-How and Patent Rights within the foregoing, the "***Biogen Results***") and (b) in the case of Ionis, to the extent arising under or otherwise subject to a disclosure obligation of Ionis under this Agreement, (all Know-How and Patent Rights within the foregoing, the "***Ionis Results***" and, collectively with the Biogen Results, the "***Results***"). All intellectual property matters with respect to the Results, including any Patent Rights therein, will be governed by the intellectual property provisions of this Agreement, and the Know-How and Patent Rights included in the Ionis Results shall constitute Ionis Manufacturing and Analytical Know-How and Ionis Manufacturing and Analytical Patents, respectively, under this Agreement. If requested by either Party, Biogen and Ionis will establish a manufacturing committee to facilitate the exchange of Results between the Parties. For clarity, Biogen shall have the right, in its sole discretion, to determine whether to seek patent protection for any Biogen Results that are not jointly owned with Ionis, and Biogen shall control and be responsible for all aspects of the Prosecution and Maintenance of any Patent Right within such Biogen Results (each, a "***Biogen Manufacturing Program Patent***") in accordance with Section 7.2.2(c) of this Agreement. Biogen shall notify Ionis within 30 days if Biogen files a patent application Controlled by Biogen or its Affiliates that claims any Biogen Results and shall provide Ionis with a copy of such patent application. Ionis will have no obligation to incorporate any Biogen Results into Ionis' manufacturing processes.

(b) For clarity, the Manufacturing Process Development Terms, and not the enabling licenses set forth in Section 4.4.3 and Section 4.4.4, shall govern with respect to all Results.

ARTICLE 5.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

5.1. **Biogen Diligence**. Following Option exercise for a Collaboration Program, Biogen 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 Products under such Collaboration Program. If Biogen exercises one or more Options under this Agreement, Biogen will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize at least one Product under this Agreement.

5.1.1. **Integrated Development Plan for Products**. On a Product-by-Product basis, Biogen will prepare a Development and global integrated Product plan outlining key aspects of the Development of each Product through Approval as well as key aspects of worldwide regulatory strategy, market launch, and Commercialization, including Product sales forecasts (each, an "***Integrated Development Plan***" or "***IDP***"). Biogen will prepare the IDP for each Product no later than [***] after Option exercise for the Collaboration Program to which such Product relates. The IDP will include [***]. SCHEDULE 5.1.1 sets forth examples of the types of information Biogen expects will be available to include in the IDP at different stages of development and commercialization. Once Biogen has prepared such plans, Biogen will update the IDP consistent with Biogen's standard practice and provide such updates to Ionis [***] ([***]) [***]. Biogen and Ionis will meet [***] to discuss the draft of the IDP and Biogen will consider, in good faith, any proposals and comments made by Ionis for incorporation in the final IDP. Notwithstanding the foregoing, Biogen's obligations to provide Ionis with information or reports with respect to a Product under this Section 5.1.1 will terminate if [***].

5.1.2. **Investigator's Brochure**. Following Option exercise for a Collaboration Program, Biogen will keep Ionis reasonably informed with respect to the status, activities and progress of Development of Products under such Collaboration Program by providing a copy of the Investigator's Brochure and any updates thereto to Ionis. Biogen's obligations under this Section 5.1.2 will terminate if [***].

5.2. **Regulatory Matters**. Consistent with Section 4.7 and Section 4.9.2, if Biogen exercises an Option with respect to a Collaboration Program, Biogen shall have ownership of all INDs, NDAs, MAAs, Priority Review Vouchers, orphan drug designations and other regulatory filings and documentation with respect to Products under such Collaboration Program, and will be responsible for all communications with Regulatory Authorities regarding such Products. Subject to Section 5.2.2 and Section 5.2.3, Biogen will have sole decision-making authority with respect to the matters set forth in this Section 5.2.

5.2.1. **Participation in Regulatory Meetings**. On a Collaboration Program-by-Collaboration Program basis, following Option exercise for a particular Collaboration Program, Biogen will provide Ionis with as much advance written notice as practicable of any meetings that Biogen has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for such Product or that directly relate to Ionis' antisense oligonucleotide chemistry platform, and will allow [***] of Ionis to participate in any such meetings at the direction of Biogen; *provided*, *however*, that Biogen may exclude Ionis from any portion of such meeting that does not pertain to such Product or to Ionis' antisense oligonucleotide chemistry platform.

5.2.2. **Regulatory Communications**. On a Collaboration Program-by-Collaboration Program basis, following Option exercise for a particular Collaboration Program, Biogen will promptly provide Ionis with copies of documents and communications submitted to (including drafts thereof) and received from Regulatory Authorities [***] that materially impact the Development or Commercialization of such Product for Ionis' review and comment, and Biogen will consider in good faith including any comments provided by Ionis to such documents and communications. During such period, Biogen will promptly notify Ionis upon receipt of any such documents or communications from any Regulatory Authority [***].

5.2.3. **Class Generic Claims**. To the extent Biogen intends to make any claims in a Product label or regulatory filing that are class generic to ASOs, Biogen will provide such claims and regulatory filings to Ionis in advance and will consider in good faith any proposals and comments made by Ionis, *provided*, *however*, that Biogen is not obligated to incorporate such proposals and comments in any such claims and regulatory filings.

5.2.4. **Applicable Laws**. Biogen will perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted.

5.3. **Pharmacovigilance Agreement; Global Safety Database**.

5.3.1. **Pharmacovigilance Agreement**. No later than [***] prior to the date on which Biogen reasonably anticipates that it will exercise an Option, the Parties shall enter into a written pharmacovigilance agreement governing each Party's respective obligations with respect to safety-related matters, including matters relating to the collection, review, assessment, tracking, exchange and filing of information related to adverse events associated with such Product, on terms substantially the same as the terms of the safety data exchange agreements entered into by the Parties with respect to the ALS Collaboration Programs and Biogen Conducted Non-ALS Collaboration Programs (each as defined in the Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated October 20, 2017).

5.3.2. Ionis' Antisense Safety Database.

(a) Ionis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during preclinical and clinical development (the "***Ionis Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Ionis compounds, Biogen will cooperate in connection with populating the Ionis Internal ASO Safety Database. To the extent collected by Biogen and in the form in which Biogen uses/stores such information for its own purposes, Biogen will provide Ionis with information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to Products as soon as practicable following the date such information is available to Biogen (but not later than [***] after Biogen's receipt of such information). In connection with any reported serious adverse event, Biogen will provide Ionis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, Biogen will provide Ionis with copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within [***] following the date such information is filed or is available to Biogen, as applicable. Furthermore, Biogen will promptly provide Ionis with any supporting data and answer any follow-up questions reasonably requested by Ionis. All such information disclosed by Biogen to Ionis will be Biogen Confidential Information; *provided, however*, that Ionis may disclose any such Biogen Confidential Information to (i) Ionis' other partners pursuant to Section 5.3.2(b) below if such information is regarding class generic properties of ASOs, or (ii) any Third Party, in each case, so long as Ionis does not disclose the identity of a Product or Biogen. Biogen will deliver all such information to Ionis for the Ionis Internal ASO Safety Database to Ionis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Ionis). Biogen will also cause its Affiliates and Sublicensees to comply with this Section 5.3.2(a).

(b) From time to time, Ionis utilizes the information in the Ionis Internal ASO Safety Database to conduct analyses to keep Ionis and its partners informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Ionis identifies safety or other related issues that may be relevant to a Product (including any potential class-related toxicity), Ionis will promptly (and in no event later than five Business Days following identification by Ionis) inform Biogen of such issues and, if requested, provide the data supporting Ionis' conclusions.

5.4. Research and Manufacturing Records. Each Party shall maintain, consistent with its then-current internal policies and practices, and cause its employees and subcontractors to maintain, consistent with its internal policies and Applicable Law, for at least ten (10) years, records and laboratory notebooks, inventory, purchase and invoice records and Manufacturing records, in each case, with respect to the Products in sufficient detail and in a good scientific manner appropriate for (i) inclusion in filings with Regulatory Authorities for such Products, and (ii) obtaining and maintaining intellectual property rights and protections, including Patent Rights for such Products. Such records and laboratory notebooks shall be complete and accurate in all material respects and shall fully and properly reflect all work done, data and developments made, and results achieved. Each Party shall allow the other Party, to the extent necessary for such regulatory or intellectual property protection purposes, to inspect or copy such records, subject to redaction by such Party.

ARTICLE 6.
FINANCIAL PROVISIONS

6.1. **Up-Front Fee**. Within [***] Business Days following the Effective Date, Biogen will pay Ionis an up-front fee of $25,000,000.

6.2. **License Fee**. On an Option-by-Option basis, together with Biogen's written notice to Ionis stating that Biogen is exercising such Option in accordance with this Agreement, Biogen will pay to Ionis a license fee of (A) $[***] if such Option is for the [***] Collaboration Program, or (B) $[***] if such Option is for the [***] Collaboration Program.

6.3. **Development Milestone Payments**. On a Collaboration Program-by-Collaboration Program basis, Biogen will pay to Ionis the milestone payments as set forth in TABLE 1 below when a milestone event (each, a "***Development Milestone Event***") listed in TABLE 1 is first achieved by a Development Candidate under such Collaboration Program:

TABLE 1

Development Milestone Event	Development Milestone Event Payment for [***] Collaboration Program	Development Milestone Event Payment for [***] Collaboration Program
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]
[***]	$[***]	$[***]

6.4. **Sales Milestone Payments**. On a Collaboration Program-by-Collaboration Program basis, Biogen will pay to Ionis the milestone payments as set forth in TABLE 2 below when a milestone event (each, a "***Sales Milestone Event***", and together with the Development Milestone Events, the "***Milestone Events***") listed in TABLE 2 is first achieved by a Product under such Collaboration Program:

TABLE 2	
Sales Milestone Event	**Sales Milestone Event Payment**
Annual Worldwide Net Sales of a Product ≥ $[***]	$[***]
Annual Worldwide Net Sales of a Product ≥ $[***]	$[***]
Annual Worldwide Net Sales of a Product ≥ $[***]	$[***]
Annual Worldwide Net Sales of a Product ≥ $[***]	$[***]

6.5. Limitations on Milestone Payments; Exceptions; Notice.

6.5.1. On a Collaboration Program-by-Collaboration Program basis, each milestone payment set forth in TABLE 1 and TABLE 2 above will be paid only once upon the first achievement of the Milestone Event by a Development Candidate under such Collaboration Program, regardless of how many Development Candidates related to such Collaboration Program achieve such Milestone Event.

6.5.2. If the [***] Milestone Event is not achieved because Development activities transpired such that achievement of such Milestone Event was unnecessary or did not otherwise occur, then upon achievement of the [***] Milestone Event, the Milestone Event payment applicable to the [***] Milestone Event will also be due. Similarly, if the "*Annual Worldwide Net Sales of a Product ≥ $[***]*" Sales Milestone Event is achieved in a particular Calendar Year and the "*Annual Worldwide Net Sales of a Product ≥ $[***]*" Sales Milestone Event is also achieved in such Calendar Year, then both the "*Annual Worldwide Net Sales of a Product ≥ $[***]*" and the "*Annual Worldwide Net Sales of a Product ≥ $[***]*" Sales Milestone Event payments are due.

6.5.3. Each time a Milestone Event is achieved under this ARTICLE 6, Biogen will send Ionis a written notice thereof promptly (but no later than five Business Days) following the date of achievement of such Milestone Event and such payment will be due within [***] of the date such notice was delivered.

6.6. Royalty Payments to Ionis.

6.6.1. **Biogen Full Royalty**. As partial consideration for the rights granted to Biogen hereunder, subject to the provisions of this Section 6.6.1 and Section 6.6.2, Biogen will pay to Ionis royalties on a Collaboration Program-by-Collaboration Program basis on Annual worldwide Net Sales of Products included in the applicable Collaboration Program sold by Biogen, its Affiliates or Sublicensees, on a country-by-country basis, in each case in the amounts as follows in TABLE 3 below (the "***Biogen Full Royalty***"):

TABLE 3			
Royalty Tier	**Annual Worldwide Net Sales of Products for the applicable Collaboration Program**	**Royalty Rate for [***] Collaboration Program**	**Royalty Rate for [***] Collaboration Program**
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 ≥ $[***] but < $[***]	[***]%	[***]%
4	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%	[***]%
5	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%	[***]%
6	For the portion of Annual Worldwide Net Sales ≥ $[***] but < $[***]	[***]%	[***]%
7	For the portion of Annual Worldwide Net Sales ≥ $[***]	[***]%	[***]%

Annual worldwide Net Sales of Products will be calculated by [***].

(a) Biogen will pay Ionis royalties on Net Sales of Products [***] under Applicable Laws, and Biogen will provide reports and payments to Ionis consistent with Section 6.9. No royalties are due on Net Sales of Products arising from compassionate use and other programs providing for the delivery of Product at no cost. 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 Full Royalty Period.

(b) For purposes of clarification, any Ionis Product-Specific Patents assigned to Biogen (i) under the Original Agreement that would, but for such assignment, Cover the applicable Product, or (ii) as set forth in Section 4.2.1, will still be considered Ionis Product-Specific Patents for determining the royalty term and applicable royalty rates under this ARTICLE 6.

6.6.2. **Application of Royalty Rates**. All royalties set forth under Section 6.6.1 are subject to the provisions of this Section 6.6.2, and are payable as follows:

(a) **Full Royalty Period**. Biogen's obligation to pay Ionis the Biogen Full Royalty above with respect to a Product will continue on a country-by-country and Product-by-Product basis from the date of First Commercial Sale of such Product until the later of the date of expiration of (i) the last Valid Claim within the Licensed Patents Covering such Product in the country in which such Product is made, used or sold, [***], or (iii) the [***] anniversary of the First Commercial Sale of such Product in such country (such royalty period, the "***Full Royalty Period***").

(b) **Competition from Generic Products**. Subject to Section 6.6.2(d), on a country-by-country and Product-by-Product basis, if, within the [***] a Generic Product is sold in a country, then the Biogen Full Royalty rate used to pay Ionis royalties on a Product in such country will be reduced to [***]% of the otherwise applicable Biogen Full Royalty rate. For the purpose of determining the [***] for a particular Product under this Section 6.6.2(b), if requested by Biogen, Ionis and Biogen will meet and confer and mutually agree upon the Parties' best estimate of when the Full Royalty Period [***] in each country where Products are being sold.

(c) **Reduced Royalty Period**. Subject to Section 6.6.2(d), on a country-by-country and Product-by-Product basis, after the expiration of the Full Royalty Period and until the end of the Reduced Royalty Period, in lieu of the royalty rates set forth in TABLE 3 of Section 6.6.1, Biogen will pay Ionis royalty rates (the "***Biogen Reduced Royalty***") on Net Sales of Products calculated on a Calendar Year-by-Calendar Year basis by [***]; *provided*, *however*, that the Biogen Reduced Royalty rate in each country will in no event exceed the [***].

(d) **Limitation on Aggregate Reductions and Offsets for Biogen Royalties**.

(i) **Aggregate Royalty Reductions**. In no event will the aggregate royalty reductions under Section 6.6.2(b) and Section 6.6.2(c) reduce the royalties payable to Ionis on Net Sales of a Product in any given period to an amount that is less than the [***] for such Product.

(ii) **Aggregate Royalty Offsets During Full Royalty Period**. During the Full Royalty Period, in no event will the aggregate royalty offsets under Section 6.8.2(b) and Section 6.8.3 reduce the royalties payable to Ionis on Net Sales of a Product in any given period to an amount that is less than the greater of (i) [***], and (ii) [***], *provided* that Biogen shall have the right to carry forward as offsets against future royalties payable to Ionis with respect to the applicable Product, any amounts that but for this Section 6.6.2(d)(ii), Biogen would have been entitled to deduct from any royalty payments to Ionis.

(iii) **Aggregate Royalty Offsets During Reduced Royalty Period**. During the Reduced Royalty Period, in no event will the aggregate royalty offsets under Section 6.8.2(b) and Section 6.8.3 reduce the royalties payable to Ionis on Net Sales of a Product in any given period to an amount that is less than the greater of (i) [***], and (ii) [***], *provided* that Biogen shall have the right to carry forward as offsets against future royalties payable to Ionis with respect to the applicable Product, any amounts that but for this Section 6.6.2(d)(iii), Biogen would have been entitled to deduct from any royalty payments to Ionis.

(e) **End of Royalty Obligation for Products**. On a country-by-country and Product-by-Product basis, other than [***], Biogen's obligation to make royalty payments hereunder for such Product in such country will end on the expiration of the Reduced Royalty Period for such Product in such country. "***Reduced Royalty Period***" means, on a country-by-country and Product-by-Product basis, the period commencing upon the expiration of [***] in such country and ending when the [***].

(f) **Royalty Examples**. SCHEDULE 6.6.2(f) attached hereto contains examples of how royalties will be calculated under this Section 6.6.

(g) **Allocation of Net Sales**. If, by reason of one or more royalty rate adjustments under this Section 6.6.2, different royalty rates apply to Net Sales of a Product from different countries, Biogen will [***] such Net Sales [***]. SCHEDULE 6.6.2(g) attached hereto contains examples of how Net Sales of such Product from different countries at different royalty rates will be [***].

6.7. **Reverse Royalty Payments to Biogen for a Discontinued Product**.

6.7.1. **Reverse Royalty for a Discontinued Product**. If Ionis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which Biogen has paid Ionis a license fee under Section 6.2, then, following the First Commercial Sale of such Discontinued Product by Ionis or its Affiliates or Sublicensees, Ionis will pay Biogen or its designated Affiliate a royalty of [***]% of Annual worldwide Net Sales of such Discontinued Product ("***Reverse Royalties***"). Ionis' obligation to pay Biogen Reverse Royalties will [***].

6.7.2. **Applicable Royalty Provisions**. In addition to this Section 6.7, the definition of Net Sales in APPENDIX 1 and the other provisions contained in this ARTICLE 6 governing payment of royalties from Biogen to Ionis will govern the payment of Reverse Royalties from Ionis to Biogen under this Section 6.7, *mutatis mutandis*, including the provisions of Sections 6.6.2, 6.8, 6.9, 6.10, 6.11, and 6.12.

6.8. Third Party Payment Obligations.

6.8.1. Existing Ionis In-License Agreements.

(a) Certain of the Licensed Technology Controlled by Ionis as of the Effective Date licensed to Biogen under Section 4.1.1 is in-licensed or acquired by Ionis under the agreements with Third Party licensors or sellers listed on SCHEDULE 6.8.1 or in a separate written agreement between the Parties (all such license or purchase agreements being the "***Ionis In-License Agreements***"), and certain milestone or royalty payments and license maintenance fees may become payable by Ionis to such Third Parties under the Ionis In-License Agreements based on the Development and Commercialization of a Product by Biogen under this Agreement.

(b) Any payment obligations arising under the Ionis In-License Agreements as existing on the Effective Date, as they apply to Products, will be paid by [***] as [***].

6.8.2. New Third Party Agreements Prior to Development Candidate Designation.

(a) If, prior to the designation of a Development Candidate under Section 1.4.2(b) with respect to a Collaboration Program, either Party becomes aware of Third Party Patent Rights or Know-How that are necessary to Develop, Manufacture or Commercialize a Product under such Collaboration Program, Ionis will seek to obtain a sublicensable license under such Third Party Patent Rights or Know-How. If Ionis obtains such a license, such Third Party Patent Rights or Know-How shall automatically be deemed "Licensed Technology" under this Agreement, and any payment obligations arising under such license, as they apply to Products, will be paid by [***] as [***]. If any such Third Party Patent Right would have been considered an Ionis Product-Specific Patent had Ionis Controlled such Patent Right on the Effective Date, then Biogen shall have the right to review and comment on the terms of any license with respect to such Third Party Patent Right prior to execution thereof, and Ionis shall only enter into such license in the final form approved by Biogen (such approval not to be unreasonably withheld, delayed or conditioned).

(b) If Ionis fails to obtain such a license under such Third Party Patent Rights or Know-How, then Ionis will so notify Biogen, and Biogen may seek to obtain such a Third Party license. If Biogen obtains such a Third Party license, then, subject to Section 6.6.2(d), Biogen may offset an amount equal to [***]% of [***] against [***] (including pursuant to Biogen's right to carry any excess amounts forward to subsequent Calendar Quarters as set forth in Section 6.6.2(d)).

6.8.3. New Third Party Agreements Following Development Candidate Designation.

(a) Additional Ionis IP.

(i) If, following the designation of a Development Candidate under Section 1.4.2(b) with respect to a Collaboration Program, either Party becomes aware of any Additional Core IP or any Patent Right or Know-How that would have been considered an Ionis Manufacturing and Analytical Patent or Ionis Manufacturing and Analytical Know-How had Ionis Controlled such Patent Right or Know-How on the Effective Date (such Patent Rights and Know-How, "***Additional Manufacturing IP***" and, collectively with the Additional Core IP, the "***Additional Ionis IP***"), Ionis will have the first right, but not the obligation, to negotiate with and obtain a license from the Third Party Controlling such Additional Ionis IP. If Ionis obtains such a Third Party license, Ionis will include such Additional Ionis IP in the license granted to Biogen under Section 4.1.1, and any financial obligations under such Third Party agreement will be paid solely by [***] as [***].

(ii) If, however, Ionis elects not to obtain such a license to such Additional Ionis IP, Ionis will so notify Biogen, and Biogen may obtain such a Third Party license. If Biogen obtains such a Third Party license, then, subject to Section 6.6.2(d), Biogen may offset an amount equal to [***]% of [***] against [***] of this Agreement [***] (including pursuant to Biogen's right to carry any excess amounts forward to subsequent Calendar Quarters as set forth in Section 6.6.2(d)).

(iii) If it is unclear whether certain Third Party Patent Rights or Know-How constitute Additional Ionis IP, Ionis will send written notice to such effect to Biogen, 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 Ionis 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 Biogen is permitted to [***]. The costs of any Third Party expert engaged under this Section 6.8.3(a)(iii) will be paid by the Party against whose position the Third Party lawyer's determination is made.

(iv) If a Third Party Controlling Additional Ionis IP is awarded a judgment from a court of competent jurisdiction arising from its claim against Biogen asserting that [***], Biogen will be permitted to (i) [***], and (ii) [***] (in each case ((A) and (B)), subject to Biogen's right to carry any excess amounts forward to subsequent Calendar Quarters as set forth in Section 6.6.2(d)).

(b) **Other Intellectual Property**. If following the designation of a Development Candidate under Section 1.4.2(b) with respect to a Collaboration Program, either Party becomes aware of Third Party Patent Rights or Know-How that would be [***] Develop, Manufacture or Commercialize a Product under such Collaboration Program and that do not constitute Additional Ionis IP [***], then such Party will promptly provide the other Party with written notice of any such Third Party Patent Rights or Know-How, and Biogen will have the sole right, but not the obligation, to negotiate with and obtain a license from the Third Party Controlling such Third Party Patent Rights or Know-How. Except as expressly set forth in Section 7.1.3(b), if Biogen obtains such a Third Party license, and subject to Section 6.6.2(d), Biogen may offset an amount equal to [***]% of [***] against [***] (including pursuant to Biogen's right to carry any excess amounts forward to subsequent Calendar Quarters as set forth in Section 6.6.2(d)); *provided*, *however*, [***].

6.9. **Payments**.

6.9.1. **Commencement**. Beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, Biogen will make royalty payments to Ionis under this Agreement within [***] following the end of each such Calendar Quarter. Each royalty payment will be accompanied by a report, summarizing Net Sales for Products during the relevant Calendar Quarter and the calculation of royalties due thereon, including country, units, sales price and the exchange rate used and the aggregate reduction to gross sales to arrive at Net Sales. Following the end of the first full Calendar Quarter subsequent to First Commercial Sale in a Major Market of any Product (but not in any subsequent Calendar Quarter unless there is a material change in the amount of any reduction to gross sales or the methodology used by Biogen to calculate any such reduction), Biogen will also include in such report a description of the reductions to gross sales to arrive at Net Sales, broken down by each category of reduction listed in clauses (a) through (d) of the definition of "Net Sales" and a non-binding qualitative analysis describing how Biogen anticipates such reductions may fluctuate over time. If no royalties are payable in respect of a given Calendar Quarter, Biogen will submit a written royalty report to Ionis so indicating together with an explanation as to why no such royalties are payable. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for a Product is made and for each Calendar Quarter thereafter, within [***] following the end of each such Calendar Quarter, Biogen will provide Ionis a [***] report estimating the total Net Sales of, and royalties payable to Ionis for, Products projected for such Calendar Quarter.

6.9.2. **Mode of Payment**. All payments under this Agreement will be (i) payable in full in United States 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 Ionis in writing, and (iii) irrevocable, non-refundable and non-creditable. Whenever for the purposes of calculating the royalties payable under this Agreement conversion from any foreign currency will be required, all amounts will first be calculated in the currency of sale and then converted into United States dollars by applying the monthly average rate of exchange as utilized by Biogen, in accordance with GAAP, fairly applied and as employed on a consistent basis throughout Biogen's operations.

6.9.3. **Records Retention**. Commencing with the First Commercial Sale of a Product, Biogen will keep complete and accurate records pertaining to the sale of Products for a period of [***] after the year in which such sales occurred, and in sufficient detail to permit Ionis to confirm the accuracy of the Net Sales or royalties paid by Biogen hereunder.

6.10. **Audits**. After Biogen is granted a license under Section 4.1.1 for a particular Product, during the Agreement Term and for a period of [***] thereafter, at the request and expense of Ionis, Biogen will permit an independent certified public accountant of nationally recognized standing appointed by Ionis, at reasonable times and upon reasonable notice, but in no case more than [***], to examine such records as may be necessary for the purpose of verifying the calculation and reporting of Net Sales (including for purposes of determining if a milestone is due under Section 6.4) and the correctness of any royalty payment made under this Agreement for any period within the preceding [***]. As a condition to examining any records of Biogen, such auditor will sign a nondisclosure agreement reasonably acceptable to Biogen in form and substance. Any and all records of Biogen examined by such independent certified public accountant will be deemed Biogen's Confidential Information. Upon completion of the audit, the accounting firm will provide both Biogen and Ionis with a written report disclosing whether the royalty payments made by Biogen are correct or incorrect and the specific details concerning any discrepancies ("***Audit Report***"). If, as a result of any inspection of the books and records of Biogen, it is shown that Biogen's payments under this Agreement were less than the royalty amount (or sales milestone amount) which should have been paid, then Biogen will make all payments required to be made by paying Ionis the difference between such amounts to eliminate any undisputed discrepancy revealed by said inspection within 45 days of receiving the Audit Report, with interest calculated in accordance with Section 6.12. If, as a result of any inspection of the books and records of Biogen, it is shown that Biogen's payments under this Agreement were greater than the royalty amount which should have been paid, [***]; *provided*, *however*, that if [***]. Ionis will pay for such audit, except that if Biogen is found to have underpaid Ionis by more than [***]% of the amount that should have been paid, Biogen will reimburse Ionis' reasonable costs of the audit.

6.11. Taxes.

6.11.1. 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.

6.11.2. Withholding Tax. The Parties agree to cooperate with one another and use reasonable efforts to lawfully avoid or reduce tax 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. To the extent the paying Party is required to deduct and withhold taxes, interest or penalties on any payment, the paying Party will pay the amounts of such taxes to the proper governmental authority for the account of the receiving Party and remit the net amount to the receiving Party in a timely manner. The paying Party will promptly furnish the receiving Party with proof of payment of such taxes. If documentation is necessary in order to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are entitled to do so.

6.11.3. Tax Cooperation. Ionis will provide Biogen with any and all tax forms that may be reasonably necessary in order for Biogen to lawfully not withhold tax or to withhold tax at a reduced rate under an applicable bilateral income tax treaty. Following Biogen's timely receipt of such tax forms from Ionis, Biogen 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. Ionis will provide any such tax forms to Biogen upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to determine if any taxes are applicable to payments under this Agreement and 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 6.11.

The provisions of this Section 6.11 are to be read in conjunction with the provisions of Section 12.4 below.

6.12. 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.

6.13. Exclusion of Products under Original Agreement. For clarity, and notwithstanding anything to the contrary in this Agreement or the Original Agreement, irrespective of whether an [***] Compound or an [***] Compound meets the definition of a "*Compound*" as defined in the Original Agreement, if any such [***] Compound or [***] Compound is designated an [***] Development Candidate, an [***] Development Candidate, or a Backup Compound under this Agreement, then such [***] Development Candidate, [***] Development Candidate, and/or Backup Compound will be subject to the terms of this Agreement and not the terms of the Original Agreement.

ARTICLE 7.
INTELLECTUAL PROPERTY

7.1. **Ownership**.

7.1.1. **Ionis Technology and Biogen Technology**. As between the Parties, Ionis will own and retain all of its rights, title and interest in and to the Licensed Know-How and Licensed Patents and Biogen will own and retain all of its rights, title and interest in and to the Biogen Know-How and Biogen 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, Biogen is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Biogen or its Affiliates under this Agreement ("***Biogen Program Know-How***") and any Patent Rights that claim or cover Biogen Program Know-How ("***Biogen Program Patents***" and together with the Biogen Program Know-How, the "***Biogen Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by Biogen to Ionis under this Agreement. As between the Parties, Ionis is the sole owner of any Know-How discovered, developed, invented or created solely by or on behalf of Ionis or its Affiliates under this Agreement ("***Ionis Program Know-How***") and any Patent Rights that claim or cover such Know-How ("***Ionis Program Patents***" and together with the Ionis Program Know-How, the "***Ionis Program Technology***"), and will retain all of its rights, title and interest thereto, subject to any assignment, rights or licenses expressly granted by Ionis to Biogen under this Agreement. Any Know-How discovered, developed, invented or created jointly under this Agreement 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 Biogen and Ionis 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 Biogen Program Patents, Ionis 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 (the "***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, including the preparation of the intellectual property assessment to be included in each Development Candidate Data Package and the activities set forth in this ARTICLE 7, and will cooperate with respect to any such activities. Ionis' obligation to participate in the JPC will terminate upon Biogen's exercise of (or the expiration or termination of) the last Option. Thereafter, Ionis will have the right, but not the obligation, to participate in JPC meetings. In preparing the intellectual property assessment to be included in each Development Candidate Data Package, the JPC will discuss a strategy with regard to intellectual property considerations with respect to the applicable Development Candidate, including prosecution and maintenance, defense and enforcement of Ionis Product-Specific Patents that would be or are licensed to Biogen under Section 4.1.1 in connection with a Product and Biogen Product-Specific Patents, defense against allegations of infringement of Third Party Patent Rights, and licenses to Third Party Patent Rights or Know-How, in each case to the extent such matter would be reasonably likely to have a material impact on this Agreement or the Original Agreement or the licenses granted hereunder or thereunder, which strategy will be considered in good faith by the Party entitled to prosecute, enforce or defend such Patent Rights, as applicable, hereunder, but will not be binding on such Party.

(b) Ionis or Biogen (as applicable) will provide the JPC with notice of any Know-How or Patent Rights discovered, developed, invented or created jointly by such Party and a Third Party in the performance of activities under the ASO Development Candidate Identification Plan or activities under the preclinical toxicology strategy for a Collaboration Program, or solely by a Third Party performing activities under the ASO Development Candidate Identification Plan or activities under the preclinical toxicology strategy for a Collaboration Program on such Party's behalf (such Know-How and Patent Rights, the "***Collaborator IP***") promptly after such Party receives notice or otherwise becomes aware of the existence of such Collaborator IP. The JPC will determine whether any such Collaborator IP would be infringed by the Development, registration, Manufacture or Commercialization of the applicable Development Candidate or any Compound under consideration for potential designation as a Development Candidate. If the JPC (or independent patent counsel engaged pursuant to this Section 7.1.3(b)) determines that any Collaborator IP would be infringed by such Development, registration, Manufacture or Commercialization, [***]; *provided* that, [***].

Notwithstanding any provision to the contrary in this Agreement, if Collaborator IP arises from activities performed by a Third Party under the ASO Development Candidate Identification Plan or activities under the preclinical toxicology strategy for a Collaboration Program, then any payment obligations arising under the applicable [***] based on the Development or Commercialization of a Product will be paid as follows: [***].

With respect to any such Collaborator IP [***], Biogen will have the right in accordance with Section 4.1.5 to elect to exclude any such Collaborator IP from the applicable license granted to Biogen under Section 4.1.1 by providing Ionis written notice prior to Option exercise. If, prior to the date the applicable license under Section 4.1.1 is granted hereunder, Biogen provides Ionis with such a written notice to exclude certain of such Collaborator IP from such license, such Collaborator IP will not be included in the Licensed Technology licensed with respect to the applicable Products under this Agreement. If Biogen does not provide Ionis with such a written notice to exclude such Collaborator IP prior to the date the applicable license under Section 4.1.1 is granted hereunder, such Collaborator IP (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.

In case of a dispute in the JPC over whether any Collaborator IP would be infringed by the Development, registration, Manufacture or Commercialization of the applicable Development Candidate or any Compound under consideration for potential designation as the Development Candidate, at the non-contracting Party's request, 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, taking into account any existing prior art. The decision of such independent patent counsel will be binding on the Parties. Expenses of such patent counsel will be borne by the non-contracting Party.

(c) In addition, the JPC 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 JPC (or otherwise between Ionis and Biogen) over inventorship of Program Patents, if the JPC cannot resolve such dispute, 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.

(d) The JPC will comprise an equal number of members from each Party. The JPC 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 ARTICLE 7. The JPC will determine by unanimous consent 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 JPC 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 JPC 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.

7.2. **Prosecution and Maintenance of Patents**. The Parties acknowledge and agree that it is critical to the success of the Products under this Agreement and to the continued success of Spinraza®, that the Parties closely coordinate the Prosecution and Maintenance of any Patent Rights for Products under this Agreement with the Prosecution and Maintenance of the Patent Rights for Spinraza® under the Original Agreement. Such efforts will include Ionis' coordination with Biogen prior to Option exercise of Ionis' Prosecution and Maintenance of the Ionis Product-Specific Patents and any Jointly-Owned Program Patents Covering Products.

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. On a Collaboration Program-by-Collaboration Program basis, until the earlier of the date Biogen is granted the license under Section 4.1.1 and the expiration or termination of Biogen's right to be granted such license, Ionis will use Commercially Reasonable Efforts to diligently Prosecute and Maintain all Ionis Product-Specific Patents and any Jointly-Owned Program Patents Covering Products, in each case to the extent that Ionis has the right to Prosecute and Maintain such Patent Rights.

7.2.2. Licensed Patents and Biogen Patents.

(a) **Licensed Patents In General**. Prior to the date Biogen is granted the license under Section 4.1.1 for a Product, Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of all Licensed Patents that are the subject of such license grant, subject to Section 7.2.2(b) and Section 7.2.3; *provided* if Biogen reasonably believes that Ionis' planned Prosecution and Maintenance of a Product-Specific Patent that would be subject to a license granted to Biogen under Section 4.1.1, is reasonably likely to adversely affect the scope, validity or enforceability of a Product-Specific Patent Covering Spinraza® under the Original Agreement, then the Parties through the JPC will try to develop a strategy that maximizes the protection for the potential Development Candidates under this Agreement but is not reasonably likely to adversely affect the scope, validity or enforceability of a Product-Specific Patent Covering Spinraza® under the Original Agreement. If the Parties cannot agree on such a strategy then either Party may refer the matter to (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 if Ionis' planned Prosecution and Maintenance is reasonably likely to adversely affect the scope, validity or enforceability of a Product-Specific Patent Covering Spinraza® under the Original Agreement. If such independent Third Party intellectual property lawyer believes Ionis' planned Prosecution and Maintenance is reasonably likely to adversely affect the scope, validity or enforceability of a Product-Specific Patent Covering Spinraza® under the Original Agreement, such lawyer will propose a strategy to maximize the protection for the potential Development Candidates under this Agreement but is not reasonably likely to adversely affect the scope, validity or enforceability of a Product-Specific Patent Covering Spinraza®. The determination and recommended strategy of the Third Party expert engaged under this Section 7.2.2(a) will be binding on the Parties solely for purposes of setting the Prosecution and Maintenance strategy for the relevant Product-Specific Patent under this Agreement. The costs of any Third Party expert engaged under this Section 7.2.2(a) will be paid by the Party against whose position the Third Party lawyer's determination is made. During the Agreement Term, Ionis will control and be responsible for all aspects of the Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents.

(b) **Licensed Patents After License Grant**. After the date Biogen is granted the license under Section 4.1.1 for a Product, Biogen will control and be responsible for all aspects of the Prosecution and Maintenance of all the Ionis Product-Specific Patents and Jointly-Owned Program Patents that are the subject of such license to the same extent Ionis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such license.

(c) **Biogen Patents**. During the Agreement Term, Biogen will control and be responsible for all aspects of the Prosecution and Maintenance of all Biogen Patents, subject to Section 7.2.4.

7.2.3. **Jointly-Owned Program Patents**. Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents that do not Cover Products. Prior to the date Biogen is granted the license under Section 4.1.1, Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents Covering Products that are the subject of such license. After the date Biogen is granted the license under Section 4.1.1, Biogen will control and be responsible for all aspects of the Prosecution and Maintenance of Jointly-Owned Program Patents Covering Products that are the subject of such license.

7.2.4. **Other Matters Pertaining to Prosecution and Maintenance of Patents**.

(a) Each Party will keep the other Party informed through the JPC as to material developments with respect to the Prosecution and Maintenance of the Ionis Core Technology Patents, Product-Specific Patents and 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 Biogen elects (a) not to file and prosecute patent applications for the Jointly-Owned Program Patents, Ionis Product-Specific Patents that have been licensed or assigned to Biogen under this Agreement or Biogen Product-Specific Patents ("***Biogen-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 Biogen-Prosecuted Patent in a particular country, or (c) not to file and prosecute patent applications for the Biogen-Prosecuted Patent in a particular country following a written request from Ionis to file and prosecute in such country, then Biogen will so notify Ionis promptly in writing of its intention (including a reasonably detailed rationale for doing so) in good time to enable Ionis to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and except as set forth in Section 7.2.4(c), Ionis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such Biogen-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, Biogen will cooperate with Ionis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such Biogen-Prosecuted Patent in such country in Ionis' own name, but only to the extent that Biogen is not required to take any position with respect to such abandoned Biogen-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 Biogen under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Ionis assumes responsibility for the Prosecution and Maintenance of any such Biogen-Prosecuted Patent under this Section 7.2.4(b), Ionis will have no obligation to notify Biogen if Ionis intends to abandon such Biogen-Prosecuted Patent.

(c) Notwithstanding Section 7.2.4(b) above, if, after having consulted with outside counsel, Biogen reasonably determines that filing or continuing to prosecute a patent application in a particular country for a Biogen-Prosecuted Patent (the "***Conflicting Patent Right***") is reasonably likely to adversely affect the scope, validity or enforceability of a patent application or issued patent in a particular country for another Biogen-Prosecuted Patent (the "***Superior Patent Right***"), in each case where both the Conflicting Patent Right and the Superior Patent Right if issued would meet the criteria set forth in clause (i) of Section 6.6.2(a), then *so long as* Biogen continues to Prosecute and Maintain the Superior Patent Right in accordance with this Agreement, Ionis will not have the right under Section 7.2.4(a) above to file or prosecute the Conflicting Patent Right.

(d) If, during the Agreement Term, Ionis intends to abandon any Ionis Product-Specific Patent for which Ionis is responsible for Prosecution and Maintenance without first filing a continuation or substitution, then, if Biogen's right to obtain a license under Section 4.1.1 to such Ionis Product-Specific Patent has not expired or terminated, Ionis will notify Biogen of such intention at least [***] days before such Patent Right will become abandoned, and Biogen 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 Biogen assumes responsibility for the Prosecution and Maintenance of any such Ionis Product-Specific Patent under this Section 7.2.4(d), Biogen will have no obligation to notify Ionis if Biogen intends to abandon such Ionis Product-Specific Patent.

(e) The Parties, through the JPC, 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.

(f) 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 [***] 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(f), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Program Patents.

(g) In addition, the Parties will consult, through the JPC, 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, Ionis and Biogen 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 Biogen Patents. Except as set forth in 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 the date the license under Section 4.1.1 is granted to Biogen, Biogen will be solely responsible for Patent Costs arising from the Prosecution and Maintenance of the Ionis 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) Ionis will have the first right, but not the obligation, to defend against any such Proceeding initiated prior to the date Biogen is granted the license under Section 4.1.1 at its sole cost and expense, and (b) Biogen will have the first right, but not the obligation, to defend against any such Proceeding initiated after the date Biogen is granted the license under Section 4.1.1 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 [***] 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, Ionis will have the first right, but not the obligation, to defend against and settle such Proceeding at its sole cost and expense. Biogen will reasonably assist Ionis in defending such Proceeding and cooperate in any such litigation at the request and expense of Ionis. Each Party may at its own expense and with its own counsel join any defense directed by the other Party. Ionis will provide Biogen with prompt written notice of the commencement of any such Proceeding, or of any allegation of infringement of which Ionis becomes aware and that is of the type described in this Section 7.4.2, and Ionis will promptly furnish Biogen with a copy of each communication relating to the alleged infringement received by Ionis.

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 (e.g., a counterclaim of infringement), 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).

7.4.4. **Effect of Defense of Third Party Claims on Original Agreement**. Notwithstanding anything to the contrary in this Section 7.4, if, prior to the date Biogen is granted the license under Section 4.1.1, Biogen reasonably believes that Ionis' election to defend against a Proceeding (and Ionis' strategy with respect to such defense) under this Section 7.4 would be reasonably likely to adversely affect a Product-Specific Patent Covering Spinraza® under the Original Agreement, then the Parties through the JPC will try to develop a strategy with respect to such defense that maximizes the protection for the potential Development Candidates under this Agreement but is not reasonably likely to adversely affect the Product-Specific Patent Covering Spinraza® under the Original Agreement. If the Parties cannot agree on such a strategy then either Party may refer the matter to (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 if Ionis' planned defense against a Proceeding (and Ionis' strategy with respect thereto) is reasonably likely to adversely affect a Product-Specific Patent Covering Spinraza® under the Original Agreement. If such independent Third Party intellectual property lawyer believes Ionis' planned defense against a Proceeding (and Ionis' strategy with respect thereto) is reasonably likely to adversely affect a Product-Specific Patent Covering Spinraza® under the Original Agreement, such lawyer will propose a strategy to maximize the protection for the potential Development Candidates under this Agreement but is not reasonably likely to adversely affect a Product-Specific Patent Covering Spinraza®. The determination and recommended strategy of the Third Party expert engaged under this Section 7.4.4 will be binding on the Parties solely for purposes of setting the defense strategy against the relevant Proceeding under this Agreement. The costs of any Third Party expert engaged under this Section 7.4.4 will be paid by the Party against whose position the Third Party lawyer's determination is made.

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 SMN 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 License Grant.

(a) For any Competitive Infringement with respect to a Product occurring after the Effective Date but before the date Biogen is granted the license under Section 4.1.1, Ionis 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 Biogen will have the right to be represented in that action by counsel of its own choice at its own expense, *provided*, *however*, Ionis will have the sole right to control such litigation; and *provided*, *further*, that, if Biogen reasonably believes that Ionis' election to institute, prosecute, and control a Proceeding with respect to such Competitive Infringement (and Ionis' strategy with respect thereto) under this Section 7.5.2 would be reasonably likely to adversely affect a Product-Specific Patent Covering Spinraza® under the Original Agreement, then the Parties through the JPC will try to develop a strategy that maximizes the protection for the potential Development Candidates under this Agreement but is not reasonably likely to adversely affect a Product-Specific Patent Covering Spinraza® under the Original Agreement. If the Parties cannot agree on such a strategy then either Party may refer the matter to (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 if Ionis' planned enforcement against a Competitive Infringement (and Ionis' strategy with respect thereto) is reasonably likely to adversely affect a Product-Specific Patent Covering Spinraza® under the Original Agreement. If such independent Third Party intellectual property lawyer believes Ionis' planned enforcement against a Competitive Infringement (and Ionis' strategy with respect thereto) is reasonably likely to adversely affect a Product-Specific Patent Covering Spinraza® under the Original Agreement, such lawyer will propose a strategy to maximize the protection for the potential Development Candidates under this Agreement but is not reasonably likely to adversely affect a Product-Specific Patent Covering Spinraza®. The determination and recommended strategy of the Third Party expert engaged under this Section 7.5.2 will be binding on the Parties solely for purposes of setting the enforcement strategy against the relevant Competitive Infringement under this Agreement. The costs of any Third Party expert engaged under this Section 7.5.2 will be paid by the Party against whose position the Third Party lawyer's determination is made.

(b) Ionis will provide Biogen with prompt written notice of the commencement of any such Proceeding, and Ionis will keep Biogen apprised of the progress of such Proceeding. If Ionis 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 Ionis has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Biogen will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice; *provided* that Ionis will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Ionis 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 Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents.

7.5.3. **Following License Grant**. For any Competitive Infringement with respect to a particular Product (except for a Discontinued Product) occurring after the date Biogen is granted the license under Section 4.1.1, so long as part of such Proceeding Biogen also enforces any Patent Rights Controlled by Biogen (including any Ionis Product-Specific Patents assigned by Ionis to Biogen under this Agreement) being infringed that Cover the Product, then Biogen 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 at its own expense, and Ionis will have the right, at its own expense, to be represented in that action by counsel of its own choice; however, Biogen will have the right to control such litigation. If Biogen 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 Biogen has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such 90 day period), Ionis will have the right to initiate and control a Proceeding with respect to such Competitive Infringement by counsel of its own choice, and Biogen will have the right to be represented in any such action by counsel of its own choice at its own expense. Notwithstanding the foregoing, Ionis 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 Ionis Core Technology Patents or Ionis Manufacturing and Analytical 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, 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 the date Biogen is granted the license under Section 4.1.1 with respect to the applicable Product will be (i) [***]; or (ii) [***]; then

(c) any remaining proceeds constituting direct or actual damages for acts of infringement occurring after the date Biogen is granted the license under Section 4.1.1 with respect to the applicable Product [***]; 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 ARTICLE 7, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 7 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 Biogen 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, [***]; 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 Ionis**. Ionis will retain all rights to pursue an infringement of any Patent Right solely owned by Ionis which is other than a Competitive Infringement and Ionis will retain all recoveries with respect thereto.

7.6.3. **Patents Solely Owned by Biogen**. Biogen will retain all rights to pursue an infringement of any Patent Right solely owned by Biogen which is other than a Competitive Infringement and Biogen will retain all recoveries with respect thereto.

7.7. **Patent Listing**.

7.7.1. **Biogen's Obligations**. Biogen will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover each Product. Prior to such listings, the Parties will meet, through the JPC, to evaluate and identify all applicable Patent Rights, and Biogen will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the JPC for any such listing. Notwithstanding the preceding sentence, Biogen will retain final decision-making authority as to the listing of all applicable Patent Rights for the Products that are not Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents, regardless of which Party owns such Patent Rights.

7.7.2. **Ionis' Obligations**. Ionis will promptly, accurately and completely list, with the applicable Regulatory Authorities during the Agreement Term, all applicable Patent Rights that Cover a Discontinued Product. Prior to such listings, the Parties will meet, through the JPC, to evaluate and identify all applicable Patent Rights, and Ionis will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by the JPC for any such listing. Notwithstanding the preceding sentence, Ionis will retain final decision-making authority as to the listing of all applicable Patent Rights for such Discontinued Products, as applicable, regardless of which Party owns such Patent Rights.

7.8. **Joint Research Agreement under the Leahy-Smith America Invents Act**. Notwithstanding anything to the contrary in this ARTICLE 7, neither Party will have the right to make an election under 35 U.S.C. § 102(c) of the Leahy-Smith America Invents Act when exercising its rights under this ARTICLE 7 without the prior written consent of the other Party, which will not be unreasonably withheld, conditioned or delayed. With respect to any such permitted election, each Party will use reasonable efforts to cooperate and coordinate their activities with the other 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 ARTICLE 7 will be subject to the Third Party rights and obligations under any (i) New Third Party License obtained in accordance with Section 6.8.2(a) or Section 6.8.3(a)(i), (ii) Prior Agreements, and (iii) Ionis In-License Agreements; *provided*, *however*, that, to the extent that Ionis has a non-transferable right to prosecute, maintain or enforce any Patent Rights licensed to Biogen hereunder and, this Agreement purports to grant any such rights to Biogen, Ionis will act in such regard with respect to such Patent Rights at Biogen's direction.

7.10. **Additional Right and Exceptions**. Notwithstanding any provision of this ARTICLE 7, Ionis retains the sole right to Prosecute and Maintain Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents during the Agreement Term and to control any enforcement of Ionis Core Technology Patents and Ionis 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 Ionis and Covering the Ionis Core Technology Patents or Ionis 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 a Product. After the date Biogen is granted the license under Section 4.1.1 with respect to a Product, Biogen will have the sole right to determine which relevant patents will be extended.

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 Preclinical Studies or Clinical Studies of the Products and its activities under each Collaboration Program.

8.2. **Representations and Warranties of Ionis**. Ionis hereby represents and warrants to Biogen, as of the Effective Date, that:

8.2.1. Ionis Controls the Licensed Patents existing as of the Effective Date and is entitled to grant all rights and licenses (or sublicenses, as the case may be) it purports to grant to Biogen under this Agreement;

8.2.2. to the best of its knowledge and belief, there are no additional licenses (beyond those that would be granted to Biogen under Section 4.1.1 upon the exercise of the Option for a Product arising under the Collaboration Programs) under any intellectual property owned or Controlled by Ionis or its Affiliates as of the Effective Date that would be required in order for Biogen to further Develop and Commercialize a Product;

8.2.3. the Licensed Technology existing as of the Effective Date constitutes all of the Patent Rights and Know-How Controlled by Ionis as of the Effective Date that are necessary to Develop, Manufacture or Commercialize the Compounds contemplated under the Collaboration Programs in the Field. Ionis has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in the Licensed Technology in a manner that conflicts with any rights granted to Biogen hereunder with respect to Products;

8.2.4. neither Ionis nor its Affiliates owns or Controls any Patent Rights or Know-How covering formulation or delivery technology as of the Effective Date that would be useful or necessary in order for Biogen to further Develop or Commercialize the Compounds contemplated under the Collaboration Programs;

8.2.5. there are no claims, judgments or settlements against or owed by Ionis or its Affiliates or pending against Ionis or, to the best of Ionis' knowledge, threatened against Ionis, in each case relating to the Ionis Manufacturing and Analytical Know-How or Ionis Know-How that could impact activities under this Agreement. To the best of Ionis' 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 Ionis Manufacturing and Analytical Know-How or Ionis Know-How that would impact activities under this Agreement;

8.2.6. SCHEDULE 8.2.6(a), SCHEDULE 8.2.6(b) and SCHEDULE 8.2.6(c) set forth true, correct and complete lists of all Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents, and Ionis Product-Specific Patents that apply to the Compounds as of the Effective Date, respectively, and indicates whether each such Patent Right is owned by Ionis or licensed by Ionis from a Third Party and if so, identifies the licensor or sublicensor from which the Patent Right is licensed. Ionis 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 Biogen under this Agreement;

8.2.7. at the Effective Date (a) there is no fact or circumstance known by Ionis that would cause Ionis to reasonably conclude that any Licensed Patent is invalid or un-enforceable, (b) there is no fact or circumstance known by Ionis that would cause Ionis to reasonably conclude the inventorship of each Licensed Patent is not properly identified on each patent, (c) all official fees, maintenance fees and annuities for the Licensed Patents have been paid and all administrative procedures with governmental agencies have been completed, and (d) none of the Licensed Patents is currently involved in any interference, reissue, re-examination, cancellation or opposition proceeding and neither Ionis, nor any of its Affiliates, has received any written notice from any Person, or has knowledge, of such actual or threatened proceeding;

8.2.8. Ionis has set forth on SCHEDULE 6.8.1 or in a separate written agreement with Biogen true, correct and complete lists of the agreements with Third Party licensors or sellers pursuant to which Ionis has licensed or acquired the Licensed Technology Controlled by Ionis as of the Effective Date that is necessary or useful to conduct the research, Development, Manufacture or Commercialization of the Products. All Ionis In-License Agreements are in full force and effect and have not been modified or amended. Neither Ionis nor, to the best knowledge of Ionis, the Third Party licensor in an Ionis In-License Agreement is in default with respect to a material obligation under such Ionis 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 Ionis In-License Agreement;

8.2.9. SCHEDULE 8.2.9 is a complete and accurate list of all agreements that create Third Party Obligations with respect to the Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents that affect the rights granted by Ionis to Biogen under this Agreement with respect to Collaboration Programs;

8.2.10. to the best of Ionis' knowledge, the Development, Manufacture (as manufactured by Ionis at its facility as of the Effective Date) and Commercialization of the Compounds or Products as contemplated by this Agreement does not [***]; and

8.2.11. as of the Effective Date, Ionis has no [***].

8.3. **Ionis Covenants**. Ionis hereby covenants to Biogen that, except as expressly permitted under this Agreement:

8.3.1. Ionis will promptly amend SCHEDULE 8.2.6(a), SCHEDULE 8.2.6(b) and SCHEDULE 8.2.6(c) and submit such amended Schedules to Biogen if Ionis becomes aware that any Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents or Ionis Product-Specific Patents are not properly identified on such Schedule.

8.3.2. during the Agreement Term, Ionis will maintain and not breach any Ionis 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 Ionis that are Controlled by Ionis and are licensed or may become subject to a license from Ionis to Biogen for a Development Candidate under this Agreement;

8.3.3. Ionis will promptly notify Biogen of any material breach by Ionis or a Third Party of any New Third Party License, and in the event of a breach by Ionis, will permit Biogen to cure such breach on Ionis' behalf upon Biogen's request;

8.3.4. Ionis will not amend, modify or terminate any Ionis In-License Agreement or New Third Party License in a manner that would adversely affect Biogen's rights hereunder without first obtaining Biogen's written consent, which consent may be withheld in Biogen's sole discretion;

8.3.5. Ionis will not enter into any new agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case that restricts, limits or encumbers the rights granted to Biogen under this Agreement;

8.3.6. Ionis will cause its Affiliates, licensees and sublicensees to comply with the terms of Section 2.1;

8.3.7. all employees and contractors of Ionis performing Development activities hereunder on behalf of Ionis will be obligated to assign all right, title and interest in and to any inventions developed by them, whether or not patentable, to Ionis or such Affiliate, respectively, as the sole owner thereof; and

8.3.8. if, after the Effective Date, Ionis becomes the owner or otherwise acquires Control of any formulation or delivery technology that would be necessary or useful in order for Biogen to further Develop, Manufacture or Commercialize a Product, and Biogen has exercised the applicable Option and the license granted to Biogen under this Agreement with respect to such Product is in effect, Ionis will make such technology available to Biogen on commercially reasonable terms.

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. BIOGEN AND IONIS 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 Biogen**. Biogen will indemnify, defend and hold harmless Ionis 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 Biogen, its Affiliates or Sublicensees and its or their respective directors, officers, employees and agents, in connection with Biogen'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 Biogen 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 Biogen or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Ionis pursuant to this Agreement); or

9.1.4. the Commercialization of a Product by or on behalf of Biogen 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 Ionis or its Affiliates, licensees, Sublicensees or contractors, and its or their respective directors, officers, employees and agents or other circumstance for which Ionis has an indemnity obligation pursuant to Section 9.2.

9.2. **Indemnification by Ionis**. Ionis will indemnify, defend and hold harmless Biogen 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 Ionis, its Affiliates or Sublicensees or its or their respective directors, officers, employees and agents, in connection with Ionis' 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 Ionis under ARTICLE 8 or any other provision under this Agreement;

9.2.3. any Development or Manufacturing activities that are conducted by or on behalf of Ionis or its Affiliates or Sublicensees (which will exclude any Development or Manufacturing activities that are conducted by or on behalf of Biogen pursuant to this Agreement); or

9.2.4. any development, manufacturing or commercialization activities that are conducted by or on behalf of Ionis 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 Biogen or its Affiliates, licensees, Sublicensees or contractors and its or their respective directors, officers, employees and agents or other circumstance for which Biogen 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. **Ionis' Insurance Obligations**. Ionis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement. Ionis will furnish to Biogen evidence of such insurance upon request.

9.4.2. **Biogen's Insurance Obligations**. Biogen 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, Biogen will maintain, in force from 30 days prior to enrollment of the first patient in a Clinical Study, a [***] 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 30 days before Biogen initiates the First Commercial Sale of a Product hereunder. Biogen will furnish to Ionis evidence of such insurance upon request. Notwithstanding the foregoing, Biogen may self-insure to the extent that it self-insures for its other products.

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 OF THIS AGREEMENT, (c) A PARTY'S BREACH OF ARTICLE 2, OR A BREACH OF SECTION 10.4.4(a) BY BIOGEN 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 this Agreement expires as follows:

10.1.1. on a country-by-country basis, on the date of expiration of all payment obligations by the Commercializing Party under this Agreement with respect to all Products (or Discontinued Products) in such country;

10.1.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to all Products (or Discontinued Products) in all countries pursuant to Section 10.1.1;

10.1.3. where no Development Candidates have been designated by the expiration of the ASO Development Candidate Identification Term as described in Section 1.9; and

10.1.4. where every Option has expired as a result of Biogen not providing Ionis a written notice stating Biogen is exercising such Options and paying Ionis the applicable license fees under Section 6.2 by the Option Deadline.

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. **Biogen's Termination for Convenience**. At any time following payment by Biogen of the up-front fee under Section 6.1, subject to Section 10.4.1 below, Biogen may terminate this Agreement for convenience, in its entirety or on a Collaboration Program-by-Collaboration Program or Product-by-Product basis, at any time by [***] days' written notice to Ionis of such termination.

10.2.2. **Termination for Failure to Divest Directly Competitive Product**. If a Competing Acquirer does not, during the Divestiture Period, divest itself of a Directly Competitive Product, terminate the development and commercialization of such Directly Competitive Product or assign this Agreement to a Third Party that is not itself developing or commercializing a Directly Competitive Product as set forth in Section 12.5, Biogen may terminate this Agreement immediately upon providing written notice to Ionis.

10.2.3. Termination Due to Failure to Obtain HSR Clearance.

(a) If the Parties make an HSR Filing with respect to a Collaboration Program under Section 3.3 of this Agreement and the HSR Clearance Date has not occurred on or prior to [***] days after the effective date of the latest HSR Filing made by the Parties, this Agreement will terminate solely with respect to the applicable Collaboration Program (i) at the election of either Party immediately upon notice to the other Party, if the FTC or the DOJ has instituted (or threatened to institute) any action, suit or proceeding including seeking, threatening to seek or obtaining a preliminary injunction under the HSR Act against Biogen and Ionis to enjoin or otherwise prohibit the transactions contemplated by this Agreement related to such Collaboration Program, or (ii) at the election of either Party, immediately upon notice to the other Party, if the Parties have not resolved any and all objections of the FTC and DOJ as contemplated by Section 3.3.2. Notwithstanding the foregoing, this Section 10.2.3 will not apply if an HSR Filing is not required to fully perform this Agreement with respect to a proposed Collaboration Program.

(b) If Biogen has paid the up-front fee under Section 6.1 and this Agreement is terminated with respect to a Collaboration Program in accordance with Section 10.2.3(a), then, *until* [***] as follows:

(i) If Ionis [***]; and

(ii) If (a) Ionis, (b) its Affiliates or (c) the licensee [***].

Nothing in this Section 10.2.3(b) obligates Ionis to (y) [***] or (z) [***]. For clarity, Ionis' rights to (1) [***] or (2) [***] are subject to the provisions of ARTICLE 2 of this Agreement.

10.2.4. Termination for Material Breach.

(a) **Biogen's Right to Terminate**. If Biogen believes that Ionis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under ARTICLE 1, which is governed by Section 10.2.5 below), then Biogen may deliver notice of such material breach to Ionis. If the breach is curable, Ionis will have [***] days to cure such breach. If Ionis fails to cure such breach within the [***]-day period, or if the breach is not subject to cure, Biogen in its sole discretion may terminate this Agreement with respect to the Collaboration Program affected by such breach by providing written notice to Ionis. 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 Collaboration Program affected by such breach.

(b) **Ionis' Right to Terminate**. On a Product-by-Product basis, if Ionis believes that Biogen is in material breach of (i) a payment obligation under ARTICLE 6 with respect to a Product or (ii) one or more material provisions of this Agreement with respect to a Product, where such material breaches have occurred multiple times over the course of at least a [***]-month period (where such material breach is not a single continuous event) demonstrating a pattern of failing to timely comply with Biogen's obligations under this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 5.1, which is governed by Section 10.2.5 below), then Ionis may deliver notice of such material breach with respect to such Product to Biogen. If the breach is curable, Biogen will have [***] 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 [***] days following such notice). If Biogen fails to cure such breach within the [***]-day or [***]-day period, as applicable, or if the breach is not subject to cure, Ionis in its sole discretion may terminate this Agreement with respect to the Collaboration Program affected by such breach by providing written notice to Biogen.

10.2.5. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Ionis, in Biogen's reasonable determination, fails to use Commercially Reasonable Efforts in the activities contemplated in ARTICLE 1 prior to the date Biogen is granted a license under Section 4.1.1 with respect to a Collaboration Program, Biogen will notify Ionis and, within [***] days thereafter, Ionis and Biogen 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 Ionis' use of Commercially Reasonable Efforts in ARTICLE 1. Following such a meeting, Ionis will have [***] days to cure such outstanding issues related to its use of Commercially Reasonable Efforts. If by the end of the [***]-day period, Ionis fails to use Commercially Reasonable Efforts as contemplated by ARTICLE 1 with respect to the applicable Collaboration Program, then subject to Section 10.2.6 below, Biogen will have the right, at its sole discretion, to (i) terminate this Agreement as it relates to the applicable Collaboration Program, or (ii) if the breach involves a Collaboration Program prior to Option exercise, trigger the alternative remedy provisions of Section 10.3 below as it relates to the applicable Collaboration Program in lieu of terminating this Agreement for such Collaboration Program by providing written notice to Ionis.

(b) If Biogen, in Ionis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 5.1 above, Ionis will notify Biogen and, within [***] days thereafter, Ionis and Biogen 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 Biogen's use of Commercially Reasonable Efforts in Section 5.1. Following such a meeting, Biogen will have [***] days to cure such outstanding issues related to its use of Commercially Reasonable Efforts. If by the end of the [***]-day period, Biogen fails to use Commercially Reasonable Efforts as contemplated by Section 5.1, then subject to Section 10.2.6 below, Ionis will have the right, at its sole discretion, to terminate this Agreement.

10.2.6. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 10.2.4 or Section 10.2.5 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 [***]-day period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 10.2.4 or Section 10.2.5, or trigger the alternative remedy provisions of Section 10.3, 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 [***] 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.

10.2.7. Termination for Insolvency.

(a) 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.

(b) 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.

10.2.8. **Termination for Patent Challenge**. Ionis may terminate this Agreement if Biogen (i) commences or otherwise voluntarily determines to participate in any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Licensed Patents, or (ii) directs, supports or actively assists any other Person in bringing or prosecuting any action or proceeding challenging or denying the validity of any claim within an issued patent or patent application within such Licensed Patents and, in each case ((i) or (ii)), within [***] days' written notice from Ionis, Biogen fails to rescind any and all of such actions, *provided however* that, nothing in this clause prevents Biogen from taking any of the actions referred to in this clause and *provided further* that Ionis will not have the right to terminate if Biogen:

(a) takes any such action as described in clause (i) or (ii) above as may be necessary or reasonably required to assert a cross-claim or a counter-claim or to respond to a court request or order or administrative law request or order, including asserting invalidity as a defense in any court proceeding brought by Ionis asserting infringement of a Licensed Patent; or

(b) Acquires a Third Party that has an existing challenge, whether in a court or administrative proceeding, against a Licensed Patent; or

(c) licenses a product for which Ionis has an existing challenge, whether in a court or administrative proceeding, against a Licensed Patent.

10.3. **Alternative Remedies to Termination Available to Biogen Prior to Option Exercise**. If, prior to Option exercise with respect to a particular Collaboration Program, Biogen elects to exercise the alternative remedy provisions of this Section 10.3 in lieu of terminating this Agreement for such Collaboration Program by providing written notice of such election to Ionis in accordance with Section 10.2.5(a), then, solely with respect to the Collaboration Program giving rise to Biogen's exercise of these alternative remedy provisions, this Agreement will continue in full force and effect with the following modifications:

(a) Ionis will have no further rights or obligations to Develop the Product under the applicable Collaboration Program or participate in the JSC, JPC or any other subcommittees or working groups established pursuant to this Agreement. Biogen will solely make all decisions that this Agreement would otherwise require or permit the JSC, JPC or any other subcommittees or working groups, or the Parties collectively, to make; *provided*, *however*, that Biogen will not have the right to create any obligations or incur any liabilities for or on behalf of Ionis;

(b) effective as of the date of Biogen's notice to Ionis electing the alternative remedy provisions of this Section 10.3, Biogen will be deemed for all purposes of this Agreement to have exercised the applicable Option;

(c) Biogen will have and Ionis grants, the exclusive license granted to Biogen under Section 4.1.1 for the applicable Collaboration Program;

(d) Biogen may exclude Ionis from all discussions with Regulatory Authorities regarding the applicable Products, except to the extent Ionis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law;

(e) Biogen's obligation to make further disclosures of Know-How or other information to Ionis regarding the applicable Products pursuant to this Agreement (including pursuant to Section 4.9) will terminate, other than reports required by Section 6.9.1, Section 10.4.3 (if applicable), and as reasonably required to permit Ionis to perform its obligations under this Agreement; *provided* such remedy will not limit or diminish the scope of any licenses granted by Biogen to Ionis under this Agreement; and

(f) Ionis will perform its obligations under Section 4.9 with respect to the applicable Product within [***] days of Biogen electing to exercise its alternative remedies under this Section 10.3, and will provide to Biogen and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Biogen in assuming complete responsibility for the Development and Manufacture of the applicable Products in an efficient and orderly manner.

10.4. Consequences of Expiration or Termination of the Agreement.

10.4.1. 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 Product 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 for a surviving Product or Spinraza®. 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) **No Effect on Original Agreement**. For clarity, the expiration or termination of this Agreement shall not modify the rights and obligations of the Parties under the Original Agreement.

(d) **Survival**. The following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 1.9 (End of ASO Development Candidate Identification Term); Section 1.10 (Carryover Development Candidates); ARTICLE 2 (Exclusivity Covenants) (solely to the extent set forth in Section 2.4 (Exclusivity Under Original Agreement)); Section 3.2 (Option and Option Deadline) (but only with respect to each Party's transfer obligations thereunder); Section 4.1.3 (Effect of Termination on Sublicenses); Section 4.2.2 (Grant Back to Ionis); Section 4.3 (Data Licenses); Section 4.4.3 (Enabling License to Biogen); Section 4.4.4 (Enabling License to Ionis); Section 4.5 (Licenses to Ionis for Biogen Results); Section 4.6 (Right to Obtain Direct License from Biogen to Ionis Partner; Sublicensees of Ionis); Section 4.7.2 (Priority Review Vouchers) (but not in the case where this Agreement is terminated under Section 10.2.2, Section 10.2.4(a) or Section 10.2.5(a)); Section 5.4 (Research and Manufacturing Records); Section 6.7 (Reverse Royalty Payments to Biogen for a Discontinued Product); Section 6.9.3 (Records Retention); Section 6.10 (Audits); Section 6.13 (Exclusion of Products under Original Agreement); Section 7.1.1 (Ionis Technology and Biogen Technology); Section 7.1.2 (Agreement Technology); Section 8.4 (Disclaimer); ARTICLE 9 (Indemnification; Insurance); Section 10.2.3(b); Section 10.2.7 (Termination for Insolvency); Section 10.4 (Consequences of Expiration or Termination of the Agreement) (except Section 10.4.5 (Remedies Available to Biogen after Ionis' Material Breach After Option Exercise)); ARTICLE 11 (Confidentiality); ARTICLE 12 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

10.4.2. **Natural Expiration**. If this Agreement expires in accordance with Section 10.1.1 or Section 10.1.2, the following terms will apply to any Product that is the subject of such expiration:

(a) **Perpetual, Royalty-Free Non-Exclusive License**. If Biogen has been granted a license under Section 4.1.1 for a particular Product, then upon expiration of the Reduced Royalty Period for such Product in all countries in which such Product is being or has been sold, Ionis will and hereby does grant to Biogen a perpetual, non-exclusive, worldwide, royalty-free, fully paid-up, sublicensable license under the Ionis Know-How to Manufacture, Develop and Commercialize the applicable Product.

10.4.3. **Termination Before License Grant**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 before Biogen has been granted a license under Section 4.1.1 for a particular Product, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to each Product or Collaboration Program that is the subject of such expiration or termination:

(a) Biogen's Option under ARTICLE 3 will expire.

(b) Solely in the event that this Agreement expires or is terminated by a Party in its entirety or upon termination of both Collaboration Programs without Option exercise by Biogen, Ionis will be free to Develop and Commercialize the applicable Product (and any other applicable Compounds or other ASOs designed to bind to the RNA that encodes SMN) on its own or with a Third Party, subject to the provisions of Section 1.10 and ARTICLE 2 of this Agreement.

(c) Solely in the event that this Agreement expires or is terminated by a Party in its entirety or upon termination of both Collaboration Programs without Option exercise by Biogen, neither Party will have any further obligations under Section 2.1 of this Agreement, except as expressly set forth in Section 2.4 of this Agreement.

(d) Solely in the event that this Agreement expires or is terminated by a Party in its entirety or upon termination of both Collaboration Programs without Option exercise by Biogen, to the extent requested by Ionis, Biogen will promptly (1) assign to Ionis any manufacturing agreements with a CMO identified by Ionis to which Biogen is a party, solely to the extent such manufacturing agreements relate to the Collaboration Programs, and (2) 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 under the Collaboration Programs in the possession of Biogen and its contractors to the extent such data, results and information were generated by or on behalf of Biogen under this Agreement; and Ionis will pay all out-of-pocket direct Third Party costs and expenses in transferring such data, results and information together with Biogen's FTE Cost in transferring such data, results and information.

(e) Except as explicitly set forth in Section 10.4.1(a) or 10.4.1(b), Biogen will have no further rights and Ionis will have no further obligations with respect to the terminated Products and Collaboration Programs.

(f) If this Agreement is terminated in its entirety by Biogen for convenience, then:

(i) Biogen will, and does hereby, grant to Ionis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, to all Biogen Technology Controlled by Biogen 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 Ionis in accordance with Section 4.1.2, *mutatis mutandis*); and

(ii) Within 30 days following the date of the termination, Biogen will assign, and hereby does assign, to Ionis all of Biogen's right, title and interest in and to all Regulatory Materials, including any IND and orphan drug designation that relate to the applicable Discontinued Product(s), *provided* that, (x) notwithstanding the foregoing, and subject to the provisions of Section 2.1, the Parties acknowledge that Biogen shall be permitted to use excerpts or portions of any such assigned Regulatory Materials in any other regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction related to products under the Ionis/Biogen Additional Agreements or products that do not include an Oligonucleotide as an active pharmaceutical ingredient, *provided*, *further* that, for such products that do not include an Oligonucleotide as an active pharmaceutical ingredient, such excerpts or portions shall not include any Confidential Information of Ionis, and (y) for clarity, such assignment of Biogen's right, title and interest in and to such Regulatory Materials shall not include the assignment of any Know-How (including any data) contained therein. If Biogen intends to use any excerpt or portion of any such assigned Regulatory Materials in accordance with clause (x) of the preceding sentence, Biogen shall, at least 30 days in advance of the anticipated submission of such excerpt or portion to a Regulatory Authority, notify Ionis of such intent and provide to Ionis a copy of such proposed excerpt or portion for review and comment. The Parties shall discuss in good faith any comments of Ionis with respect to such proposed excerpt or portion prior to submission thereof.

10.4.4. **Termination After License Grant**. If this Agreement is terminated by a Party in accordance with this ARTICLE 10 after Biogen has been granted a license under Section 4.1.1 for a particular Product, then, in addition to the terms set forth in Section 10.4.1, the following terms will apply to any Product or Collaboration Program that is the subject of such termination:

(a) The applicable licenses granted by Ionis to Biogen under this Agreement will terminate. Biogen, its Affiliates and Sublicensees will cease selling the applicable Products, unless Ionis elects to have Biogen continue to sell the applicable Products as part of the Transition Services to the extent provided in Section 10.4.6.

(b) Solely in the event that this Agreement expires or is terminated by a Party in its entirety, neither Party will have any further obligations under Section 2.1 of this Agreement, except as expressly set forth in Section 2.4 of this Agreement.

(c) Except as explicitly set forth in Section 10.4.1(a), Biogen will have no further rights and Ionis will have no further obligations with respect to the terminated Product and Collaboration Program(s).

(d) If (i) Biogen terminates the Agreement under Section 10.2.1 (Biogen's Termination for Convenience) or (ii) Ionis terminates this Agreement under Section 10.2.4(b) (Ionis' Right to Terminate) or Section 10.2.5 (Remedies for Failure to Use Commercially Reasonable Efforts), in each case, in its entirety, then the following additional terms will also apply:

(i) Biogen will, and does hereby, grant to Ionis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, to all Biogen Technology Controlled by Biogen as of the date of such reversion that Covers the Discontinued Product(s) solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize the Discontinued Product(s) in the Field (such license will be sublicensable by Ionis in accordance with Section 4.1.2, *mutatis mutandis*);

(ii) Within 60 days following the date of the termination, Biogen will assign back to Ionis any Product-Specific Patents and Ionis' interest in any Program Patents that relate to the applicable Discontinued Product(s) previously assigned by Ionis to Biogen under this Agreement;

(iii) Within 60 days following the date of the termination, Biogen will transfer to Ionis solely for use with respect to the Development and Commercialization of the applicable Discontinued Product(s), any Know-How, data, results and copies of Regulatory Materials in the possession of Biogen 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 4.9, *provided* that, for the avoidance of doubt, as between the Parties, title to any intellectual property that is Biogen Technology within any of the foregoing will remain with Biogen subject to the license granted to Ionis under Section 10.4.4(d)(i), except as otherwise provided in Section 10.4.4(d)(iv) below;

(iv) Within [***] days following the date of the termination, Biogen will assign, and hereby does assign, to Ionis all of Biogen's right, title and interest in and to all Regulatory Materials, including any NDA, IND and orphan drug designation that relate to the applicable terminated Product(s), *provided* that, (x) notwithstanding the foregoing, and subject to the provisions of Section 2.1, the Parties acknowledge that Biogen shall be permitted to use excerpts or portions of any such assigned Regulatory Materials in any other regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction related to products under the Ionis/Biogen Additional Agreements or products that do not include an Oligonucleotide as an active pharmaceutical ingredient, *provided, further* that, for such products that do not include an Oligonucleotide as an active pharmaceutical ingredient, such excerpts or portions shall not include any Confidential Information of Ionis, and (y) for clarity, such assignment of Biogen's right, title and interest in and to such Regulatory Materials shall not include the assignment of any Know-How (including any data) contained therein. If Biogen intends to use any excerpt or portion of any such assigned Regulatory Materials in accordance with clause (x) of the preceding sentence, Biogen shall, at least 30 days in advance of the anticipated submission of such excerpt or portion to a Regulatory Authority, notify Ionis of such intent and provide to Ionis a copy of such proposed excerpt or portion for review and comment. The Parties shall discuss in good faith any comments of Ionis with respect to such proposed excerpt or portion prior to submission thereof;

(v) Biogen will, and does hereby, exclusively license to Ionis any trademarks that are specific to the Discontinued Product(s) solely for use with such Discontinued Product(s); *provided*, *however*, in no event will Biogen have any obligation to license to Ionis any trademarks used by Biogen both in connection with the Product and in connection with the sale of any other product or service, including any BIOGEN- or BIOGEN-formative marks;

(vi) Ionis will control and be responsible for all aspects of the Prosecution and Maintenance of all Jointly-Owned Program Patents arising from the terminated Product and/or Collaboration Program, and Biogen will provide Ionis with (and will instruct its counsel to provide Ionis with) all of the information and records in Biogen's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Program Patents; *provided*, *however*, if Ionis intends to abandon any such Jointly-Owned Program Patents without first filing a continuation or substitution, then Ionis will notify Biogen of such intention at least [***] days before such Patent Right will become abandoned, and Biogen 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; and

(vii) Ionis will have the obligation to pay royalties to Biogen under Section 6.7 with respect to the Discontinued Product(s). Such payments will be governed by the financial provisions in Section 6.8.3(b), and the definition of Net Sales will apply to sales of Discontinued Product(s) by Ionis, in each case *mutatis mutandis*.

(e) If Ionis terminates this Agreement in its entirety due to Biogen's material breach or Biogen terminates this Agreement in its entirety for convenience, upon Ionis' written request pursuant to a mutually agreed supply agreement, Biogen will sell to Ionis any bulk API, Clinical Supplies and Finished Drug Product with respect to the Discontinued Product(s) in Biogen's possession at the time of such termination, at a price equal to [***].

(f) Solely in the event that this Agreement expires or is terminated by a Party in its entirety, to the extent requested by Ionis, Biogen will promptly assign to Ionis any manufacturing agreements solely to the extent related to the Discontinued Product(s) and identified by Ionis to which Biogen is a party.

10.4.5. Remedies Available to Biogen for Ionis' Material Breach After Option Exercise.

(a) **Termination of Committees and Information Sharing**. If, after Option exercise, Ionis materially breaches this Agreement and fails to cure such breach within the time periods set forth under Section 10.2.4(a) or Section 10.2.5(a), and Biogen does not wish to terminate this Agreement in its entirety (an "***Ionis Breach Event***"), then, in addition to any other remedies Biogen may have under this Agreement or otherwise, Biogen will have the right to do any or all of the following in Biogen's discretion *solely with respect to the Collaboration Programs that are the subject of the Ionis Breach Event*:

(i) terminate Ionis' right to participate in the JPC, which will be disbanded (except to the extent it is performing activities under an Ionis/Biogen Additional Agreement);

(ii) terminate Ionis' participation in any ongoing research and development programs under the applicable Collaboration Program and Biogen's funding obligations associated therewith;

(iii) solely make all decisions required or permitted to be made by the JPC or the Parties collectively under this Agreement in connection with the Development and Commercialization of the applicable Product; *provided*, *however*, that Biogen will not have the right to create any obligations or incur any liabilities for or on behalf of Ionis;

(iv) exclude Ionis from all discussions with Regulatory Authorities regarding applicable Products, *except* to the extent Ionis' participation is required by a Regulatory Authority or is otherwise reasonably necessary to comply with Applicable Law;

(v) terminate Biogen's obligation to make further disclosures of Know-How or other information to Ionis pursuant to this Agreement related to the applicable Products, including pursuant to Section 4.9 and Section 5.3.2, other than reports required by Section 6.9.1, Section 10.4.4 (if applicable), and as reasonably required to permit Ionis to perform its obligations under this Agreement; *provided* such remedy will not limit or diminish the scope of any licenses granted by Biogen to Ionis under this Agreement; and

(vi) if Ionis has not completed the activities that are its responsibility under the Collaboration Programs, then Biogen may, but will not be obligated to, assume all responsibility for all such activities that would have otherwise been Ionis' responsibility under this Agreement.

Ionis will cooperate with the foregoing and provide to Biogen and its Third Party contractors all Know-How, assistance, assignments and other support reasonably requested to assist Biogen in assuming complete responsibility for the Development and Manufacture of the Products in an efficient and orderly manner.

(b) **Biogen's Right of Setoff**. If there is an [***] and Biogen does not wish to [***], then, in addition to any other remedies Biogen may have under this Agreement or otherwise, Biogen may setoff against any amounts owed to Ionis pursuant to ARTICLE 6 (Financial Provisions) *solely* with respect to the Collaboration Program that is the subject of the Ionis Breach Event [***] (the "***Setoff Amount***"). If Biogen exercises its setoff right under this Section 10.4.5(b), Biogen will provide Ionis with a written certificate, signed by Biogen's Chief Financial Officer, certifying that the amount setoff by Biogen represents [***]. Notwithstanding the foregoing, if Ionis notifies Biogen in writing (a "***Setoff Dispute Notice***") that it disputes Biogen's assertion that Ionis is in material breach of this Agreement or the amount setoff by Biogen (a "***Setoff Dispute***"), then (i) both Parties will participate in the dispute resolution process set forth on SCHEDULE 10.4.5(b), and (ii) pending the Parties' agreement regarding the appropriate setoff (if any) or a determination by the Advisory Panel of the proper amount that Biogen may setoff (if any) in accordance with SCHEDULE 10.4.5(b), Biogen will pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank. If the Parties cannot settle their dispute by mutual agreement, then, in accordance with SCHEDULE 10.4.5(b) the Advisory Panel will determine (1) the amount (if any) that Biogen may setoff against future payments *solely* with respect to the Collaboration Program that is the subject of the Ionis Breach Event to Ionis going forward, and (2) whether any portion of the escrow account should be released to Ionis or returned to Biogen, *provided* that any decision or determination by the Advisory Panel (a "***Panel Decision***") will not be treated as an arbitral award but will be binding on the Parties until and unless a court of competent jurisdiction (the "***Trial Court***") has determined in a judgment regarding some or all of the issues decided in the Panel Decision, and in any Action contemplated by the next sentence hereof the Trial Court will determine the facts and the law *de novo*, and will give a Panel Decision only such persuasive effect, if any, that after review of all of the facts and the law presented to the Trial Court by the Parties, the Trial Court deems appropriate, *provided*, that the escrow agent will comply with a Panel Decision that determines that any portion of the escrow account should be released to Ionis or returned to Biogen. If it is determined in a judgment by the Trial Court that Ionis owes Biogen any damages, then, during the pendency of any appeal of the Trial Court's decision (or, if the Trial Court's decision is not appealed, until Biogen recoups such amount), Biogen may setoff against any future payments *solely* with respect to the Collaboration Programs that are the subject of the Ionis Breach Event to Ionis under this Agreement the amount of any such damages not paid by Ionis. If it is determined in a Trial Court that Biogen has setoff an amount that exceeds the amount of losses, damages and expenses actually incurred by Biogen as a result of Ionis' breach of this Agreement, then Biogen will promptly pay Ionis the amount of such excess, plus interest on such amount as provided for in Section 6.12 (Interest), with interest accruing from the time Biogen applied such excess setoff. If, with respect to a Setoff Dispute, Ionis provides a Setoff Dispute Notice to Biogen and Biogen fails to do any of the following: (X) appoint a member of the Advisory Panel to the extent required in Section 2 of SCHEDULE 10.4.5(b); (Y) meet with the Advisory Panel as required in Section 3 of SCHEDULE 10.4.5(b); or (Z) pay the Setoff Amount into an interest-bearing escrow account established for the purpose at a bank, then Biogen will forfeit its right to set off under this Section 10.4.5(b) and SCHEDULE 10.4.5(b) with respect to any and all Setoff Disputes.

10.4.6. Transition Services. In the case where (i) Biogen terminates this Agreement in its entirety under Section 10.2.1 (Biogen's Termination for Convenience) or (ii) Ionis terminates this Agreement in its entirety under Section 10.2.4(b) (Ionis' Right to Terminate) or Section 10.2.5 (Remedies for Failure to Use Commercially Reasonable Efforts), the terms of this Section 10.4.6 shall apply.

(a) In such event, the Parties wish to provide a mechanism to ensure that patients who were being treated with a Product prior to such termination or who desire access to a Product can continue to have access to such Product while the regulatory and commercial responsibilities for such Product are transitioned from Biogen to Ionis. As such, Ionis may request Biogen perform transition services as listed on SCHEDULE 10.4.6 and such other transition services that the Parties mutually agree in writing to (1) provide patients with continued access to the applicable Products, (2) transition the responsibilities under all Approvals and ongoing Clinical Studies for the applicable Product to Ionis or its designee, and (3) transition the then-current supply process and responsibilities for the Products to Ionis or its designee (collectively, the "***Transition Services***"). Subject to the Parties agreeing on a transition plan as described in Section 10.4.6(b), Biogen will perform such Transition Services using reasonable efforts for a period not to exceed [***] months from the termination date; *provided* that Biogen and Ionis may mutually agree to conduct the Transition Services for a longer period of time. Notwithstanding the provision of the Transition Services under this Section 10.4.6(a), Ionis shall not conduct activities with respect to any Discontinued Products to the extent prohibited by ARTICLE 2 of this Agreement.

(b) Ionis may elect to have Biogen perform the Transition Services by providing written notice to Biogen no later than 30 days following the effective date of the termination. If Ionis requests Transition Services, then Ionis shall propose a transition plan setting forth the Transition Services to be performed by Biogen, including delivery and transition dates consistent with those set forth on SCHEDULE 10.4.6, and, for a period of 30 days after such request, the Parties will use good faith efforts to negotiate a mutually agreeable version of such transition plan. In addition, the Parties will, within 30 days after such request, establish a transition committee consisting of at least each Party's Alliance Managers, a representative from each Party's chemistry, manufacturing and controls (CMC) group who was responsible for the Products prior to the termination, and up to two additional representatives from each Party who are from other relevant functional groups to facilitate a smooth transition. While Biogen is providing Transition Services, Biogen and Ionis will mutually agree on talking points and a communication plan to customers, specialty pharmacies, physicians, Regulatory Authorities, patient advocacy groups, and clinical study investigators, and Biogen will make all such communication to such entities in accordance with the mutually agreed talking points.

(c) Ionis will pay Biogen for the Transition Services at [***]% of Biogen's internal costs to perform the Transition Services, calculated using the same methodology as Biogen used to calculate such expenses for such Product in its most recently audited financial statements prior to the termination date. In addition, Ionis will reimburse [***]% of Biogen's out-of-pocket costs to perform the Transition Services. Ionis will own all revenue derived from the Products after the termination date and Biogen will remit all such revenues to Ionis no later than the [***] day following the end of the month in which such revenue was received.

(d) Ionis or its designee will be sufficiently prepared to accept the transition of Development, Manufacturing and Commercialization activities with respect to the Products to Ionis or such designee on the timelines set forth on SCHEDULE 10.4.6 for the Transition Services. Biogen will have no liability under this Agreement with respect to a failure of or delay in the Transition Services to the extent caused by any failure or delay by Ionis or its designee in accepting the transition of Development, Manufacturing and Commercialization activities with respect to the Products. In the event that Biogen encounters any delays beyond Biogen's reasonable control, the Parties shall discuss in good faith and agree upon extended timelines for completion of the Transition Services.

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 or the Original 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. **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 11.3 below), complying with applicable governmental regulations, obtaining Approvals, conducting Preclinical Studies or Clinical Studies, marketing the Products, 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.

11.3. **Press Release; Publications; Disclosure of Agreement**.

11.3.1. **Public Announcements**. On or promptly after the Effective Date, the Parties will jointly issue a public announcement of the execution of this Agreement in form and substance mutually agreed by the Parties. Except to the extent required to comply with Applicable Law, regulation, rule or legal process or as otherwise permitted in accordance with this Section 11.3, neither Party nor such Party's Affiliates will make any public announcements, press releases or other public disclosures concerning 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.

11.3.2. **Use of Name**. Except as set forth in Section 11.3.8, 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.

11.3.3. **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 Biogen's sales projections) so the Parties may analyze the need for or desirability of publicly disclosing or reporting such event.

11.3.4. **Prior to License Grant**. Prior to the date Biogen has been granted a license under Section 4.1.1 with respect to a Product, such Product is the sole property of Ionis and, subject to the provisions of this Section 11.3.4, Ionis will have the sole right to issue press releases, publish, present or otherwise disclose the progress and results regarding such Product to the public, which shall be consistent with its practice with its other compounds and products; *provided* that, with respect to any proposed press release or other similar public communication by Ionis disclosing regulatory discussions or data or results arising from a Collaboration Program or Development activities under this Agreement, or that may be reasonably anticipated to impact Spinraza®, (i) Ionis will submit such proposed communication to Biogen for review at least two Business Days in advance of such proposed public disclosure, (ii) Biogen will have the right to review and recommend changes to such communication, (iii) Ionis will in good faith consider any changes that are timely recommended by Biogen, and (iv) to the extent such communication discloses data or results arising from a Collaboration Program or Development activities, (x) if Biogen informs Ionis that such communication contains Biogen Confidential Information, then Ionis will delete such Biogen Confidential Information from such communication, and (y) if Biogen informs Ionis that such communication would disclose inventions made by either Party in the course of a Collaboration Program or Development activities under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such communication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by Biogen, then Ionis will either (a) delay such proposed publication for up to 60 days from the date Biogen informed Ionis of its objection to such communication, to permit the timely preparation and first filing of patent application(s) on the information involved or (b) remove the identified disclosures prior to the publication of such communication.

11.3.5. **After License Grant**. After the date Biogen has been granted a license under Section 4.1.1 with respect to a Product, subject to the provisions of this Section 11.3.5, Biogen will have the sole right to issue press releases, publish, present or otherwise disclose the progress and results regarding such Product to the public, which shall be consistent with its practice with its other compounds and products; *provided* that with respect to any proposed press release or other similar public communication by Biogen disclosing regulatory discussions, Biogen's sales projections or data or results arising from a Collaboration Program or Development activities under this Agreement, (i) Biogen will submit such proposed communication to Ionis for review at least two Business Days in advance of such proposed public disclosure, (ii) Ionis will have the right to review and recommend changes to such communication, (iii) Biogen will in good faith consider any changes that are timely recommended by Ionis, and (iv) to the extent such communication discloses data or results arising from a Collaboration Program or Development activities, (x) if Ionis informs Biogen that such communication contains Ionis Confidential Information, then Biogen will delete such Ionis Confidential Information from such communication, and (y) if Ionis informs Biogen that such communication would disclose inventions made by either Party in the course of a Collaboration Program or Development activities under this Agreement that have not yet been protected through the filing of a patent application, or the public disclosure of such communication could be expected to have a material adverse effect on any Patent Rights or Know-How solely owned or Controlled by Ionis, then Biogen will either (a) delay such proposed publication for up to 60 days from the date Ionis informed Biogen of its objection to such communication, to permit the timely preparation and first filing of patent application(s) on the information involved or (b) remove the identified disclosures prior to the publication of such communication.

11.3.6. **Scientific or Clinical Presentations for Products**. Regarding any proposed scientific publications or public presentations related to summaries of data or results arising from a Collaboration Program or Development activities under this Agreement, the Parties acknowledge that scientific lead time is a key element of the value of the Products under this Agreement and further agree to use Commercially Reasonable Efforts to control public scientific disclosures of such data or results, to prevent any potential adverse effect of any premature public disclosure of such data or results. The Parties will establish a procedure for publication review and each Party will first submit to the other Party through the JPC an early draft of all such publications or presentations, whether they are to be presented orally or in written form, at least [***] days prior to submission for publication including to facilitate the publication of any summaries of such data or results as required on the clinical trial registry of each respective Party, as applicable. 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 Collaboration Programs. If, during such [***]-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 [***]-day period, the other Party informs such Party that its proposed publication discloses inventions made by either Party in the course of a Collaboration Program or Development activities 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 [***] 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. With respect to each Clinical Study, Biogen shall determine authorship or attribution with respect to any proposed publications regarding the results of such Clinical Study, by interpreting and applying the authorship and attribution principles of the International Committee of Medical Journal Editors' *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals*.

11.3.7. **SEC Filings**. Each Party will give the other Party a reasonable opportunity to review all material filings with the SEC describing the terms of this Agreement prior to submission of such filings, and will give due consideration to any reasonable comments by the non-filing Party relating to such filing.

11.3.8. **Subsequent Disclosure**. Notwithstanding the foregoing, to the extent information regarding this Agreement or a 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.

11.3.9. **Acknowledgment**. Each Party will acknowledge in any press release, public presentation or publication regarding the Collaboration Programs or a Product, the other Party's role in discovering and developing the Product or Discontinued Product, as applicable, that the Product is under license from Ionis and otherwise acknowledge the contributions from the other Party, and each Party's stock ticker symbol (e.g., Nasdaq: IONS, BIIB).

(a) Biogen understands and acknowledges the importance to Ionis of continuing to be associated with the drugs it discovers under the Collaboration Programs. As such, Biogen agrees that it will use reasonable efforts to prominently acknowledge Ionis' role in the discovery of a Product in any scientific, medical and other Product-related communications to the extent such communications address the research, discovery or commercialization of a Product, by prominently including the words "*Discovered by Ionis*" or equivalent language (collectively, the "***Ionis Attribution Language***") in any such communications; *provided*, *however*, that Biogen shall have no obligation to include the Ionis Attribution Language in any of the following: (i) communications or materials where such inclusion would be prohibited by Applicable Laws or applicable Third Party institutional, corporate or other policies; (ii) communications that Biogen does not control, such as publications with non-Biogen lead authors; (iii) materials primarily focused on or directed to patients, or other materials where Biogen branding is not prominently featured; or (iv) abstracts or other communications with a word limitation, if Biogen reasonably determines that such word limitation would preclude the inclusion of the Ionis Attribution Language, *provided* that, in each case, Biogen will use reasonable efforts to have the Ionis Attribution Language included in any such communication, consistent with the efforts that Biogen uses to have statements regarding its own contributions to the Product included in such communication.

(b) Ionis may include the Products (and identify Biogen as its partner for the Products) in Ionis' drug pipeline.

ARTICLE 12.
MISCELLANEOUS

12.1. Dispute Resolution.

12.1.1. Escalation. In the event of any Dispute (other than a Setoff Dispute, which Setoff Dispute will be resolved pursuant to Section 12.1.3, or dispute regarding the construction, validity or enforcement of either Party's Patent Rights, which disputes will be resolved pursuant to Section 12.2), either Party may, within [***] days after either Party notifies the other Party that the Dispute has not been resolved (*provided*, that such notice cannot be given less than [***] days after the Dispute has arisen), make a written request that the Dispute be referred for resolution to the Executive Vice President, Business Development of Biogen and the Chief Operating Officer of Ionis (the "***Executives***"). Within [***] days of either Party's written request that the Dispute be referred to the Executives, the Executives will meet in person at a mutually acceptable time and location or by means of telephone or video conference to negotiate a settlement of a Dispute. If the Executives fail to resolve the Dispute within such [***]-day period, then the Dispute will be referred to mediation under Section 12.1.2.

12.1.2. Mediation. If a Dispute subject to Section 12.1.1 cannot be resolved pursuant to Section 12.1.1, or if neither Party timely makes the written request that the Dispute be referred to the Executives, the Parties will resolve any such Dispute in accordance with the dispute resolution procedures set forth in SCHEDULE 12.1.2.

12.1.3. Setoff Disputes. Setoff Disputes will be resolved in accordance with Section 10.4.5(b) and SCHEDULE 10.4.5(b).

12.1.4. Technical Failure. If Biogen disagrees with Ionis' determination that a Technical Failure has occurred under Section 1.2, Biogen may refer the matter to an independent qualified Third Party expert accepted by both Parties for final resolution of the dispute. The expert will use the information, materials and data provided to her or him by either Party to promptly resolve the dispute. The decision of the expert will be binding upon both Parties. The Parties will equally share the costs of the expert. Should the Parties fail to agree on the expert within 10 days following either Party's request to nominate an expert under this Section 12.1.4, each Party will nominate an independent expert (who will not be a current or former employee of a Party or any of their Affiliates or have any personal or financial interest in a Party or any of their Affiliates), and promptly thereafter, those two independent experts will agree on the Third Party expert to resolve the dispute in accordance with this Section 12.1.4. In the event of any expert proceeding under this Section 12.1.4, Ionis will not be required to conduct the applicable ASO Development Candidate Identification Plan during the pendency of such proceeding.

12.2. Governing Law; Jurisdiction; Venue; Service of Process.

12.2.1. This Agreement and any Dispute will be governed by and construed and enforced in accordance with the laws of the State of Delaware, U.S.A., without reference to conflicts of laws principles.

12.2.2. Subject to the provisions of Section 12.1, each Party by its execution hereof, (a) hereby irrevocably submits to the exclusive jurisdiction of the United States District Court for the District of Delaware (or, if but only if such court lacks, or will not exercise, subject matter jurisdiction over the entirety of a Dispute, the Court of Chancery of the State of Delaware, or, if but only if such court lacks, or will not exercise, subject matter jurisdiction over the entirety of a Dispute, the Superior Court of the State of Delaware, with respect to the Dispute) for the purpose of any Dispute arising between the Parties in connection with this Agreement (each, an "***Action***") and (b) hereby waives to the extent not prohibited by Applicable Law, and agrees not to assert, by way of motion, as a defense or otherwise, in any such Action, any claim that it is not subject personally to the jurisdiction of the above-named courts, that venue in the above-named courts is improper, that its property is exempt or immune from attachment or execution, that any such Action brought in the above-named courts should be dismissed on grounds of forum non conveniens, should be transferred or removed to any court other than the above-named courts, or should be stayed by reason of the pendency of some other proceeding in any other court other than the above-named courts, or that this Agreement or the subject matter hereof may not be enforced in or by such courts and (c) hereby agrees not to commence any such Action other than before the above-named courts. Notwithstanding the previous sentence, a Party may commence any Action in a court other than the above-named court solely for the purpose of enforcing an order or judgment issued by the above-named court.

12.2.3. Each Party hereby agrees that service of process: (a) made in any manner permitted by Delaware law, or (b) made by overnight express courier service (signature required), prepaid, at its address specified pursuant to Section 12.7, will constitute good and valid service of process in any such Action and (c) waives and agrees not to assert (by way of motion, as a defense, or otherwise) in any such Action any claim that service of process made in accordance with clause (a) or (b) does not constitute good and valid service of process.

12.3. **Remedies**. Notwithstanding anything to the contrary in this Agreement, each Party will be entitled to seek, in addition to any other right or remedy it may have, at law or in equity, a temporary restraining order or a preliminary injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Agreement, and the Parties agree that in the event of a threatened or actual material breach of this Agreement injunctive relief would be appropriate. 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). Except for the offsets and credits explicitly set forth in Section 6.10 and Section 10.4.5(b), neither Party will have the right to setoff 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 consent of the other, which will not be unreasonably withheld, delayed or conditioned, [***]; *provided*, if Biogen transfers or assigns this Agreement to [***] described in this Agreement, then Biogen (or such Affiliate), will [***] due Ionis under ARTICLE 6 for the [***] such that Ionis receives [***] or assignment. In addition, Ionis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without Biogen's consent, to an Affiliate or to a Third Party in connection with a payment factoring transaction. Any purported assignment or transfer made in contravention of this Section 12.4 will be null and void.

The [***].

To the extent Ionis utilizes a [***] in any year, Ionis will [***] to Biogen [***]. To assist Biogen in determining when [***] pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which Biogen [***] payment under this Section 12.4, and each year thereafter (including, for clarity, all years in which Ionis utilizes [***]), Ionis will provide Biogen with Ionis' Annual tax returns (federal and state) and, in years in which Ionis utilizes [***], supporting documentation for such [***]. Notwithstanding the foregoing, if the [***].

12.5. **Change of Control**.

12.5.1. On a Collaboration Program-by-Collaboration Program basis, if, at any time during the applicable Option Period, a Change of Control occurs involving Ionis and a Person that, at the time of the close of such Change of Control, is developing in human clinical trials or commercializing a Directly Competitive Product within the Field or is engaged in a Directly Competitive Collaboration Program (such pre-existing Directly Competitive Product, a "***Pre-Existing Competitive Product***") or, at any time during the Agreement Term after the closing of such Change of Control, develops or acquires a Directly Competitive Product or begins a Directly Competitive Collaboration Program (such Person being hereinafter referred to as a "***Competing Acquirer***") and such Competing Acquirer has not, within [***] of either (i) the closing of the Change of Control in the event the Directly Competitive Product is being developed in human clinical trials or commercialized, or the Directly Competitive Collaboration Program exists, as of such closing date or (ii) the date of first development or acquisition of such Directly Competitive Product or the date on which such Competing Acquirer begins such Directly Competitive Collaboration Program (the "***Divestiture Period***") divested itself of the Directly Competitive Product or Directly Competitive Collaboration Program, or terminated development and commercialization of such Directly Competitive Product or such Directly Competitive Collaboration Program, then (A) Ionis will provide written notice to Biogen of the closing of such Change of Control or Divestiture Period, as applicable, (B) [***]; (C) solely with respect to any Collaboration Program that relates to such Directly Competitive Product or Directly Competitive Collaboration Program for which Initiation of IND-Enabling Toxicology Studies have not occurred, subject to Section 12.5.2, elect to have Ionis complete Ionis Activities under this Agreement for such Collaboration Program until such time as the applicable Collaboration Program is ready to begin IND-Enabling Toxicology Studies, after which Biogen may elect to exercise its rights under clause (D) of this Section 12.5.1 with respect to such Collaboration Program (in which case the applicable deadline for Biogen's notice under such clause will be extended until [***] after designation of a Development Candidate for such Collaboration Program), and (D) Biogen will have the right, within [***] following such written notice, to either:

(a) if unexercised, exercise the applicable Option by notifying Ionis in writing of Biogen's election to license the applicable Product at a prorated license fee payment as compared to the license fee payment set forth in Section 6.2, based upon the stage of Development of the applicable Product at the time of Change of Control or Divestiture Period, as applicable, which license fee payment shall be negotiated by the Parties in good faith at the time of such notification by Biogen. If Biogen exercises the applicable Option pursuant to this Section 12.5, [***]. Upon Biogen's exercise of its Option pursuant to this Section 12.5.1(a), Biogen will be deemed to have obtained and Ionis will be deemed to have granted the license set forth in Section 4.1.1; or

(b) Allow such [***]-day period to lapse without providing any such notice of election under this Section 12.5, or otherwise provide Ionis with written notice within such period electing not to exercise the applicable Option pursuant to Section 12.5.1(a) above, in either of which cases Ionis and Biogen will continue to exercise their rights and perform their respective obligations with respect to the applicable Product under the terms of this Agreement.

Upon Biogen's exercise of the applicable Option pursuant to Section 12.5.1(a) above, Ionis will carry out its technology transfer obligations pursuant to Section 4.9 with respect to the applicable Product. Provided that Ionis complies with Section 12.5.2, except as expressly set forth in Section 10.2.2, Biogen's rights as set forth in this Section 12.5.1 shall be Biogen's exclusive remedies for the failure of a Competing Acquirer to divest or terminate development and commercialization of a Directly Competitive Product or Directly Competitive Collaboration Program during the Divestiture Period in accordance with this Section 12.5.1, and the development or commercialization of a Pre-Existing Competitive Product by a Competing Acquirer will not be a violation of Ionis' exclusivity covenants under Section 2.1.1. For the avoidance of doubt, except as set forth in this Section 12.5.1, all other terms and conditions of this Agreement will apply to any such license granted pursuant to Biogen's exercise of its rights hereunder.

12.5.2. At any time while Ionis is conducting activities pursuant to Section 12.5.1, to separate its Development activities under this Agreement from development activities relating to a Directly Competitive Product ("***Directly Competing Development Activities***"), Ionis will, and will cause the Competing Acquirer to, (a) establish separate teams to conduct Development activities under this Agreement and such Directly Competing Development Activities, (b) prevent any Know-How that is Confidential Information relating to the Development of the applicable Product from being disclosed to, or used by, individuals performing such Directly Competing Development Activities and (c) not use or reference any Know-How that is Confidential Information or conduct any activities Covered by any Patent Rights, in each case Controlled by Ionis or its Affiliates prior to the effective date of the Change of Control in the development, manufacture or commercialization of the Directly Competitive Product.

12.6. **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.

12.7. **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), electronic mail 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 Ionis, addressed to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: Chief Operating Officer E-mail: [***]
with a copy to:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attention: General Counsel E-mail: [***]
If to Biogen, addressed to:	Biogen MA Inc. 225 Binney Street Cambridge, MA 02142 Attention: Vice President Corporate Development E-mail: [***]
with a copy to:	Biogen MA Inc. 225 Binney Street Cambridge, MA 02142 Attention: Chief Legal Officer E-mail: [***]
and:	Ropes & Gray LLP Prudential Tower 800 Boylston Street Boston, MA 02199-3600 Attention: Susan Galli, Esq. E-mail: [***]

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 electronic mail 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.

12.8. **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) is a comprehensive and integrated statement of the agreement between the Parties with respect to the subject matter hereof. For the avoidance of doubt, except as expressly set forth in Section 2.4 and Section 4.2.3 with respect to the Original Agreement, this Agreement in no way supersedes, modifies or otherwise affects any of the Ionis/Biogen Additional Agreements, which will remain in full force and effect in accordance with each of their respective terms. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties with respect to the subject matter hereof 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 GAAP (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 and Appendices hereto 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 and good laboratory and clinical practices and cGMP 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.

BIOGEN MA INC.

By: /s/ Michel Vounatsos
Name: Michel Vounatsos
Title: Chief Executive 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.

IONIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Chief Operating Officer

[Signature Page to Research Collaboration, Option and License Agreement]

List of Appendices and Schedules

APPENDIX 1 – Definitions

APPENDIX 2 – Development Candidate Checklist

APPENDIX 3 – ASO Development Candidate Identification Plans

SCHEDULE 1.3.1 – JSC Governance

SCHEDULE 1.3.5 – Alliance Management Activities

SCHEDULE 1.5 – List of [***]

SCHEDULE 4.9.2(C) – Ionis' Fully Absorbed Cost of Goods Methodology

SCHEDULE 5.1 – Biogen's Development and Commercialization Activities

SCHEDULE 5.1.1 - Integrated Development Plan Content

SCHEDULE 6.6.2(f) – Royalty Calculation Examples

SCHEDULE 6.6.2(g) – Allocation of Net Sales

SCHEDULE 6.8.1 – Ionis In-License Agreements

SCHEDULE 6.8.3(b) – Royalty Rate Reduction Example

SCHEDULE 8.2.6(a) – Ionis Core Technology Patents

SCHEDULE 8.2.6(b) – Ionis Manufacturing and Analytical Patents

SCHEDULE 8.2.6(c) – Ionis Product-Specific Patents

SCHEDULE 8.2.9 – Prior Agreements

SCHEDULE 10.4.5(b) – Advisory Panel Regarding Setoff Disputes

SCHEDULE 10.4.6 – Transition Services

SCHEDULE 12.1.2 – Mediation

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"***Action***" has the meaning set forth in Section 12.2.2.

"***Additional Core IP***" means Third Party intellectual property that is necessary to [***]. For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***].

"***Additional Ionis IP***" has the meaning set forth in Section 6.8.3(a)(i).

"***Additional Manufacturing IP***" has the meaning set forth in Section 6.8.3(a)(i).

"***Advisory Panel***" has the meaning in SCHEDULE 10.4.5(b) of this Agreement.

"***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 Ionis 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 1.3.5.

"***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 cGMP 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 Biogen (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 [***] Oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is at least six bases long and that modulates expression or splicing of a gene target via the binding, partially or wholly, of such compound to the RNA of such gene target.

"***ASO Development Candidate Identification Plan***" means, with respect to each Collaboration Program, the initial draft plan to identify a Development Candidate under such Collaboration Program. The ASO Development Candidate Identification Plans have been mutually agreed to by the Parties as of the Effective Date and attached hereto as APPENDIX 3, and may be modified from time to time as determined by the JSC to address the discovery, research and optimization activities that Ionis will conduct under the applicable Collaboration Program.

"***ASO Development Candidate Identification Term***" has the meaning set forth in Section 1.2.

"***Audit Report***" has the meaning set forth in Section 6.10.

"***Backup Compound***" has the meaning set forth in Section 1.4.2(b).

"***Bankruptcy Code***" has the meaning set forth in Section 10.2.7(b).

"***Biogen***" has the meaning set forth in the Preamble of this Agreement.

"***Biogen Activities***" means, under an ASO Development Candidate Identification Plan or high-level preclinical toxicology strategy, any and all research, preclinical and/or clinical activities that Biogen agrees to conduct; *provided* that Biogen will be deemed to have agreed to conduct any activities designated as Biogen Activities under any ASO Development Candidate Identification Plan it approves.

"***Biogen-Approved Costs***" has the meaning set forth in Section 1.8.

"***Biogen Full Royalty***" has the meaning set forth in Section 6.6.1.

"***Biogen Know-How***" means any Know-How owned, used, developed by, or licensed to Biogen or its Affiliates, in each case to the extent Controlled by Biogen or its Affiliates on the Effective Date or at any time during the Agreement Term, *but specifically excluding* the Biogen Program Know-How.

"***Biogen Manufacturing Program Patent***" has the meaning set forth in Section 4.9.3.

"***Biogen Patents***" means any Patent Rights included in the Biogen Technology.

"***Biogen Product-Specific Patents***" means all Product-Specific Patents owned, used, developed by, or licensed to Biogen or its Affiliates, in each case to the extent Controlled by Biogen or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***Biogen Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Biogen Program Patents***" has the meaning set forth in Section 7.1.2.

"***Biogen Program Technology***" has the meaning set forth in Section 7.1.2.

"***Biogen-Prosecuted Patents***" has the meaning set forth in Section 7.2.4.

"***Biogen Reduced Royalty***" has the meaning set forth in Section 6.6.2(c).

"***Biogen Results***" has the meaning set forth in Section 4.9.3.

"***Biogen Supported Pass-Through Costs***" means [***].

"***Biogen Technology***" means the Biogen Program Technology, Jointly-Owned Program Technology, Biogen Product-Specific Patents and any trademarks described in Section 4.1.6, owned, used, developed by, or licensed to Biogen or its Affiliates that is necessary or useful to Develop, register, Manufacture or Commercialize a Product.

"***Biogen's FTE Cost***" means the FTE Rate applicable to Biogen, *multiplied* by the applicable number of FTEs.

"[***] ***ASO Product***" has the meaning set forth in Section 2.1.2(a)(iv).

"***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 period of three (3) consecutive months ending on the last day of March, June, September, or December, respectively, and will also include the period beginning on the Effective Date and ending on the last day of the Calendar Quarter in which the Effective Date falls.

"***Calendar Year***" means a year beginning on January 1 (or, with respect to 2017, the Effective Date) and ending on December 31.

"***Carryover Development Candidate***" has the meaning set forth in Section 1.10.

"***Carryover Period***" has the meaning set forth in Section 1.10.
"***cGMP***" 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.

"***Change of Control***" means, with respect to Ionis, (a) a merger or consolidation of Ionis with a Third Party which results in the voting securities of Ionis outstanding immediately prior thereto ceasing to represent at least 50% of the combined voting power of the surviving entity immediately after such merger or consolidation, (b) a transaction or series of related transactions in which a Third Party, together with its Affiliates, becomes the owner of 50% or more of the combined voting power of Ionis' outstanding securities, (c) the sale or other transfer to a Third Party of all or substantially all of Ionis' business to which the subject matter of this Agreement relates, or (d) the stockholders or equity holders of Ionis will approve a plan of complete liquidation of Ionis or an agreement for the sale or disposition by Ionis of all or a substantial portion of its assets, other than pursuant to the transaction as described above or to an Affiliate. Notwithstanding the foregoing, the sale or issuance of shares in exchange for cash for purposes of a *bona fide* financing will not constitute a Change of Control.

"***Claims***" has the meaning set forth in Section 9.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Trial, Phase 2 Trial, Phase 3 Trial or Phase 4 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 Program***" means (a) a collaboration program between Biogen and Ionis focused on the discovery, designation of, and preclinical research for a Development Candidate that is an [***] Compound (the "[***] ***Collaboration Program***") and (b) a collaboration program between Biogen and Ionis focused on the discovery, designation of and preclinical research for a Development Candidate that is an [***] Compound (the "[***] ***Collaboration Program***"), in each case in accordance with the applicable ASO Development Candidate Identification Plan and high-level preclinical toxicology strategy.

"***Collaborator IP***" has the meaning set forth in Section 7.1.3(b).

"***Collaborator License***" has the meaning set forth in Section 7.1.3(b).

"***Commercialize***," "***Commercialization***", "***Commercializing***" or "***Commercial***" 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 such Product and studies to provide improved formulation and Product delivery, and launching and promoting such Product in each country.

"***Commercializing Party***" means (a) Biogen, with respect to a Product that is being Developed and Commercialized by or on behalf of Biogen, its Affiliates or Sublicensees hereunder, and (b) Ionis, with respect to a Discontinued Product that is being Developed and Commercialized by or on behalf of Ionis, 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 (including Spinraza®), 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 Biogen's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to perform the "[***]" described in [***], and Commercially Reasonable Efforts as it applies to Ionis' performance hereunder includes use of Commercially Reasonable Efforts to [***].

"***Competing Acquirer***" has the meaning set forth in Section 12.5.1.

"***Competitive Infringement***" has the meaning set forth in Section 7.5.1.

"***Complete***," "***Completed***," or "***Completion***" means, with respect to a Clinical Study, the point in time at which the primary database lock for such study has occurred and, if such study has a statistical analysis plan, the data generated based on that primary database lock under the statistical analysis plan for such study are available.

"***Compound***" means any [***] Compound or [***] Compound.

"***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.

"***Conflicting Patent Right***" has the meaning set forth in Section 7.2.4(c).

"***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 Ionis Supported Pass-Through Costs in the case of Ionis, and other than Biogen Supported Pass-Through Costs in the case of Biogen), 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 rights granted to a Person under such patent, the act of making, using or selling by such Person 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.

"***CSHL Agreement***" means that certain Amended and Restated Collaboration and License Agreement between Cold Spring Harbor Laboratory and Ionis dated October 26, 2011, as amended.

"***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 such 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 such Product to seek Approval for additional indications for such Product.

"***Development Candidate***" means an [***] Development Candidate or an [***] Development Candidate.

"***Development Candidate Data Package***" means, with respect to a [***], the [***]; *provided* such package contains the [***] and is consistent with the applicable ASO Development Candidate Identification Plan, and includes the intellectual property assessment generated by the JPC in accordance with Section 7.1.3(a). The checklist Ionis uses as of the Effective Date when reviewing potential development candidates for approval is attached hereto as APPENDIX 2.

"***Development Candidate Data Package Deficiency Notice***" has the meaning set forth in Section 1.4.2(a).

"***Development Milestone Event***" has the meaning set forth in Section 6.3.

"***Diagnostic Option***" has the meaning set forth in Section 3.4.1.

"***Directly Competing Development Activities***" has the meaning set forth in Section 12.5.2.

"***Directly Competitive Collaboration Program***" means any internal research program for which [***] or [***], with the goal of discovering and developing a Directly Competitive Product for which drug discovery activities have been initiated.

"***Directly Competitive Product***" means any product, other than a Product, that is designed to bind to or directly modulate SMN.

"***Disclosing Party***" has the meaning set forth in Section 11.1.

"***Discontinued Product***" means a Product upon termination of this Agreement in its entirety.

"***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.

"***Divestiture Period***" has the meaning set forth in Section 12.5.1.

"***DOJ***" has the meaning set forth in Section 3.3.1.

"***Draft Report***" means, with respect to an IND-Enabling Toxicology Study, an integrated, audited report containing the pharmacology, toxicology, bioanalytical and pharmacokinetic data generated from such IND-Enabling Toxicology Study.

"***Duplex Product***" means a product containing [***], which may also include [***].

"***Effective Date***" has the meaning set forth in the Recitals of this Agreement.

"***EMA***" means the European Medicines Agency and any successor entity thereto.

"[***] ***Compound***" means any ASO containing [***] that is designed to bind to the RNA that encodes SMN, where such ASO is discovered by Ionis prior to or during the ASO Development Candidate Identification Term, but excluding nusinersen and any Specified ASO Product in any form, formulation or dosage. An [***] Compound may contain other chemical modifications that are utilized in drugs in Ionis' clinical development pipeline as of the Effective Date (e.g., constrained ethyl and DNA), but does not contain chemical modifications that have not, as of the Effective Date, been administered intrathecally to non-human primates, such as [***].

"[***] ***Development Candidate***" means an [***] Compound that is designated by the JSC (or Biogen in accordance with Section 1.4.2(b)) as [***].

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union.

"***Excluded Payments***" means (i) royalty or profit sharing payments, or any other type of payment based on periodic sales of a Product; (ii) payments made in consideration of Ionis' or Ionis' Affiliate's equity or debt securities at fair market value; (iii) payments made to pay for or reimburse Ionis or Ionis' Affiliate for the fully-burdened cost of research and development; (iv) payments made to pay for or reimburse Ionis or Ionis' Affiliate for the cost of prosecuting, maintaining or defending Patent Rights; and (v) payments made to Ionis or Ionis' Affiliate to pass-through to a Third Party in satisfaction of a payment obligation Ionis or Ionis' Affiliate has to such Third Party.

"***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 4.1.5, 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 the first sale of a Product by Biogen, its Affiliate or its Sublicensee to a Third Party in a particular country after Approval of such Product has been obtained in such country.

"***FTC***" has the meaning set forth in Section 3.3.1.

"***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 Costs***" has the meaning set forth in Section 1.8.

"***FTE Rate***" means $[***] for the Calendar Year 2017. The FTE Rate will be increased each Calendar Year thereafter by the [***].

"***Full Royalty Period***" has the meaning set forth in Section 6.6.2.

"***Fully Absorbed Cost of Goods***" means the costs incurred by Ionis as determined using the methodology set forth in SCHEDULE 4.9.2(C) fairly applied and as employed on a consistent basis throughout Ionis' operations.

"***GAAP***" has the meaning set forth in the definition of Net Sales.

"***Gene-Editing Product***" means a synthetic nucleoside-containing compound that, when introduced into a cell of an organism, (a) is stably integrated within the genome or stable episome of the cell of such organism or (b) causes (or is perceived to cause) a permanent change in the genome of the cell of such organism.

"***Generic Product***" means, with respect to a particular Product (the "***Reference Product***"), one or more Third Party product(s), where (i) such Third Party product(s) (a) are approved in reliance, in whole or in part, on a prior Regulatory Approval of the Reference Product [***] (b) are determined by a Regulatory Authority to be substitutable for the Reference Product, [***] (ii) such Third Party product(s) when taken in the aggregate have a market share (measured in number of prescriptions with the numerator of such fractional share being such Third Party product(s) taken in the aggregate, and the denominator being the total of such Third Party product(s) taken in the aggregate plus such Product taken in the aggregate, as provided by IMS) during the applicable Calendar Quarter in such country of at least [***]%.

"***HSR Act***" means the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the rules and regulations promulgated thereunder.

"***HSR Clearance***" means all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Clearance Date***" means the earliest date on which the Parties have actual knowledge that all applicable waiting periods under the HSR Act with respect to the transactions contemplated under this Agreement have expired or have been terminated.

"***HSR Filing***" means filings by Biogen and Ionis with the United States Federal Trade Commission and the Antitrust Division of the United States Department of Justice of a Notification and Report Form for Certain Mergers and Acquisitions (as that term is defined in the HSR Act) with respect to the matters set forth in this Agreement, together with all required documentary attachments thereto.

"[***]" has the meaning set forth in Section 12.4.

"***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 Completion Date***" has the meaning set forth in Section 3.1.

"***Indemnitee***" has the meaning set forth in Section 9.3.

"***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 5.1.1.

"***Ionis***" has the meaning set forth in the Preamble of this Agreement.

"***Ionis Activities***" means the activities for which Ionis is designated as responsible under any ASO Development Candidate Identification Plan.

"***Ionis/Biogen Additional Agreements***" means (i) the Original Agreement, (ii) the DMPK Research, Development, Option and License Agreement between the Parties dated June 27, 2012, (iii) the Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated December 10, 2012 and (iv) the Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated September 5, 2013, in each case, as amended and/or restated from time to time.

"***Ionis Attribution Language***" has the meaning set forth in Section 11.3.9.

"***Ionis Breach Event***" has the meaning set forth in Section 10.4.5(a).

"***Ionis Core Technology Patents***" means all Patent Rights owned, used, developed by, or licensed to Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term, claiming subject matter generally applicable to ASOs, other than Ionis Product-Specific Patents or Ionis Manufacturing and Analytical Patents. A list of Ionis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 8.2.6(a) attached hereto.

"***Ionis In-License Agreements***" has the meaning set forth in Section 6.8.1.

"***Ionis Internal ASO Safety Database***" has the meaning set forth in Section 5.3.2.

"***Ionis Know-How***" means any Know-How, including any Jointly-Owned Program Know-How and Ionis Program Know-How, owned, used, developed by, or licensed to Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. Ionis Know-How does not include the Ionis Manufacturing and Analytical Know-How.

"***Ionis 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 Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. Ionis Manufacturing and Analytical Know-How does not include the Ionis Know-How.

"***Ionis 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 Ionis or its Affiliates, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Ionis Manufacturing and Analytical Patents as they related to ASOs as of the Effective Date is set forth on SCHEDULE 8.2.6(b) attached hereto. Ionis Manufacturing and Analytical Patents do not include the Ionis Product-Specific Patents or the Ionis Core Technology Patents.

"***Ionis Product-Specific Patents***" means all Product-Specific Patents, in each case to the extent Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Agreement Term. A list of Ionis Product-Specific Patents as of the Effective Date is set forth on SCHEDULE 8.2.6(c) attached hereto.

"***Ionis Program Know-How***" has the meaning set forth in Section 7.1.2.

"***Ionis Program Patents***" has the meaning set forth in Section 7.1.2.

"***Ionis Program Technology***" has the meaning set forth in Section 7.1.2.

"***Ionis Results***" has the meaning set forth in Section 4.9.3.

"***Ionis Supported Pass-Through Costs***" means [***].

"***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).

"***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.

"***JPC***" has the meaning set forth in Section 7.1.3.

"***JSC***" has the meaning set forth in Section 1.3.1.

"***JSC Decision Period***" has the meaning set forth in Section 1.4.2(b).

"[***] ***Criteria***" means, with respect to a Collaboration Program, the [***] Criteria, the criteria set forth in the ASO Development Candidate Identification Plan for such Collaboration Program [***], and such other criteria set forth in such ASO Development Candidate Identification Plan that are designated as "[***] *Criteria*" by mutual agreement of the Parties.

"[***] ***Criteria***" means, with respect to a Collaboration Program, the criteria set forth in the ASO Development Candidate Identification Plan for such Collaboration Program for [***].

"***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 Ionis Manufacturing and Analytical Know-How, and Ionis Know-How. For clarity, Licensed Know-How does not include any Know-How covering formulation technology or delivery devices.

"***Licensed Patents***" means the Ionis Product-Specific Patents, Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents and Ionis' 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. For clarity, Licensed Patents that are jointly-owned by Ionis and Biogen will count toward the calculation of the Full Royalty Period in a particular country if the use or sale of a Product by an unauthorized Third Party in such country would infringe a Valid Claim of such Licensed Patent.

"***Licensed Technology***" means any and all Licensed Patents and Licensed Know-How, but excluding all technology licensed to Ionis under the UMass Agreement or the CSHL Agreement (and Ionis is not granting a sublicense or any other rights under the UMass Agreement or the CSHL Agreement).

"***Losses***" has the meaning set forth in Section 9.1.

"***MAA***" means a marketing authorization application filed with the EMA or other European Regulatory Authority after completion of Clinical Studies to obtain Approval for a 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 or other country in Europe.

"***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 preclinical and clinical purposes, of API or Finished Drug Product.

"***Manufacturing Process Development Terms***" means Section 4.1.3(b), Section 4.4.1(a), Section 4.4.2, Section 4.5, Section 4.6, Section 4.8.2 and Section 4.9.3 of this Agreement.

"***Milestone Event***" has the meaning set forth in Section 6.4.

"***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.

"***Net Sales***" means the gross amount billed or invoiced on sales of a Product by Biogen, its Affiliates and Sublicensees, less the following: (a) customary trade, quantity, or cash discounts to non-affiliated brokers or agents to the extent actually allowed and taken; (b) amounts repaid or credited by reason of rejection or return; (c) to the extent separately stated on purchase orders, invoices, or other documents of sale, any taxes or other governmental charges levied on the production, sale, transportation, delivery, or use of such Product which is paid by or on behalf of Biogen; and (d) outbound transportation costs prepaid or allowed and costs of insurance in transit.

In any transfers of a Product between Biogen, its Affiliates and Sublicensees, Net Sales are calculated based on the final sale of such Product to an independent Third Party. If Biogen, 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. If Biogen, its Affiliates or Sublicensees uses or disposes of a Product in the provision of a commercial service, the Product is sold and the Net Sales are calculated based on the sales price of the Product to an independent Third Party during the same royalty period or, in the absence of sales, on the fair market value of the Product as determined by the Parties in good faith. Net Sales shall not include any transfers of supplies of the applicable Product for (i) use in clinical trials, Preclinical Studies or other research or development activities, or (ii) a *bona fide* charitable purpose; or (iii) a commercially reasonable sampling program.

With respect to Net Sales as it applies to royalties payable by Ionis, the Parties agree that any reasonable definition of "net sales" that is (x) customarily used in pharmaceutical industry technology licensing or collaboration contracts and (y) consistent with generally accepted accounting principles in the United States ("***GAAP***") or International Financial Reporting Standards and is subsequently agreed to by Ionis (or a Third Party acquirer or assignee) and Ionis' Sublicensee or commercialization partner in an arms-length transaction under a particular sublicense or commercialization agreement will replace the definition of Net Sales in this Agreement and will be used in calculating the royalty payment to Biogen on sales of products sold pursuant to such agreement. If Ionis uses such an alternate definition of "net sales" in a particular sublicense, (A) Ionis will include such "net sales" definition in the applicable royalty reports to assist Biogen with verifying royalty payments and (B) if such definition is not consistent with GAAP or International Financial Reporting Standards, upon Biogen's request, Ionis will reconcile the royalties calculated under such definition with GAAP or International Financial Reporting Standards.

"***New SMA Compound***" means any ASO that is designed to bind to the RNA that encodes SMN discovered by or on behalf of Ionis after the Effective Date, including any Specified ASO Product, but, until the expiration of the ASO Development Candidate Identification Term and, if applicable, the Carryover Period, excluding any [***] Compound or [***] Compound that is not a Specified ASO Product.

"***New SMA Compound Notice***" has the meaning set forth in Section 2.3.

"***New Third Party Licenses***" has the meaning set forth in Section 8.3.2.

"[***] ***Compound***" means any ASO containing a [***] that is designed to bind to the RNA that encodes SMN, where such ASO is discovered by Ionis prior to or during the ASO Development Candidate Identification Term, but excluding any Specified ASO Product.

"[***] ***Development Candidate***" means an [***] Compound that is designated by the JSC (or Biogen in accordance with Section 1.4.2(b)) as [***].

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***Oligonucleotide***" means a synthetic compound that comprises or consists of [***] and that is not a Gene-Editing Product or a Duplex Product. For clarity, [***] of Oligonucleotides [***] and Oligonucleotides [***]. Oligonucleotides may be single-stranded or may have sufficient self-complementarity to be entirely or partially double-stranded.

"***Option***" has the meaning set forth in Section 3.2.

"***Option Deadline***" has the meaning set forth in Section 3.2.

"***Option Period***" has the meaning set forth in Section 2.1.1(a).

"***Original Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Other Activities***" has the meaning set forth in Section 1.8.

"***Other ASO Product***" has the meaning set forth in Section 2.1.2(a)(iv).

"***Panel Decision***" has the meaning set forth in Section 10.4.5(b).

"***Party***" or "***Parties***" means Biogen and Ionis 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 Ionis before or after the Effective Date to any Third Party under the Ionis Core Technology Patents, the Ionis Manufacturing and Analytical Patents, or the Ionis Manufacturing and Analytical Know-How (but not under the Ionis Product-Specific Patents) to (a) use ASOs (or supply ASOs to end users) solely to conduct preclinical research, or (b) enable such Third Party to manufacture or formulate ASOs, 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) Ionis does not assist such Third Party to identify, discover or make a Compound or Product; and (2) material transfer agreements with academic collaborators or non-profit institutions solely to conduct non-commercial 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 1 Trial***" means, with respect to a Product, a first clinical study in human beings of such Product, as further defined in 21 C.F.R. 312.21(a) or the corresponding regulation in jurisdictions other than the United States.

"***Phase 2 Trial***" means, with respect to a Product, a Clinical Study that is intended to explore the feasibility, safety, dose ranging or efficacy of such Product, that is prospectively designed to generate sufficient data (if successful) to commence a Phase 3 Trial (or foreign equivalent) of such product, as further defined in 21 C.F.R. 312.21(b) or the corresponding regulation in jurisdictions other than the United States.

"***Phase 3 Trial***" means, with respect to a Product, a pivotal Clinical Study in humans performed to gain evidence with statistical significance of the efficacy of such product in a target population, and to obtain expanded evidence of safety for such product that is needed to evaluate the overall benefit-risk relationship of such product, to form the basis for approval of an NDA by a Regulatory Authority and to provide an adequate basis for physician labeling, as described in 21 C.F.R. 312.21(c), as amended from time to time, or the corresponding regulation in jurisdictions other than the United States.

"***Phase 4 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.

"***Preclinical 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 a Product and whether such Product has a desired effect.

"***Pre-Existing Competitive Product***" has the meaning set forth in Section 12.5.1.

"***Prior Agreements***" means the agreements listed on SCHEDULE 8.2.9 attached hereto.

"***Priority Review Voucher***" means a voucher or right granted by the FDA or other Regulatory Authority that allows for priority review of a potential product that is issued or granted to a sponsor of a neglected disease or rare disease product application when a product to treat a neglected disease or rare disease is approved by such Regulatory Authority.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means a finished drug product containing a Compound as an active pharmaceutical ingredient.

"***Product-Specific Patents***" means, with respect to a Product, 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 such Product, or (ii) methods of using such Product as a prophylactic or therapeutic; *provided however*, Patent Rights Controlled by Ionis or any of its Affiliates that (y) include claims that are directed to subject matter applicable to ASOs or products in general, or (z) include an ASO, the sequence of which targets the RNA that encodes SMN and the RNA of a gene that does not encode SMN, will not be considered Product-Specific Patents, and in the case of (y) and (z), such Patent Rights will be considered Ionis 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.

"***Reduced Royalty Period***" has the meaning set forth in Section 6.6.2(e).

"***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.

"***Regulatory Materials***" means, with respect to a Product, any regulatory submissions, notifications, registrations, approvals and/or other filings and correspondence made to or with a Regulatory Authority in any country or jurisdiction, and any other records required by Applicable Law to be maintained that may be necessary or useful to develop, manufacture, market, sell or otherwise commercialize such Product in any such country or jurisdiction.

"***Research***" means conducting the research activities with ASOs or Compounds as set forth in the ASO Development Candidate Identification Plan or the preclinical toxicology strategy, including preclinical research and lead optimization, *but specifically excluding* Development and Commercialization.

"***Results***" has the meaning set forth in Section 4.9.3.

"***Reverse Royalties***" has the meaning set forth in Section 6.7.1.

"***RMC***" means Ionis' Research Management Committee, or any successor committee.

"***Royalty Quotient***" has the meaning set forth in Section 6.6.2(c).

"***Sales Milestone Event***" has the meaning set forth in Section 6.4.

"***Setoff Amount***" has the meaning set forth in Section 10.4.5(b).

"***Setoff Dispute***" has the meaning set forth in Section 10.4.5(b).

"***Setoff Dispute Notice***" has the meaning set forth in Section 10.4.5(b).

"***SMN***" means (i) SMN1 or SMN2, or (ii) both SMN1 and SMN2.

"***SMN1***" means the gene, Survival of Motor Neuron 1 (GenBank accession # NM_000344; Gene ID: 6606), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***SMN2***" means the gene, Survival of Motor Neuron 2 (GenBank accession #NM_017411; Gene ID: 6607), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***Specified ASO Product***" has the meaning set forth in Section 2.1.2(a)(iv).

"***Spinal Muscular Atrophy***" means an autosomal recessive motor neuron disease primarily affecting neonates and young children that results from a loss of SMN1 (GenBank accession # NM_000344; Gene ID: 6606) protein.

"***Spinraza®***" means the nusinersen product marketed under the brand name Spinraza® in the United States, or the equivalent nusinersen product of Biogen or its Affiliates or Sublicensees in other jurisdictions, whether or not marketed under such brand name.

"***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 Biogen Technology, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***Subsequent Deal***" has the meaning set forth in Section 10.2.3(b)(i).

"***Superior Patent Right***" has the meaning set forth in Section 7.2.4(c).

"[***] ***ASO Product***" has the meaning set forth in Section 2.1.2(a)(iv).

"***Target Related Biogen Program Claim***" has the meaning set forth in Section 4.4.4.

"***Target Related Ionis Program Claim***" has the meaning set forth in Section 4.4.3.

"***Technical Failure***" has the meaning set forth in Section 1.2.

"***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 Ionis and a Third Party (including the Ionis In-License Agreements) that relate to a Product or SMN, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Transition Services***" has the meaning set forth in Section 10.4.6.

"***Trial Court***" has the meaning set forth in Section 10.4.5(b).

"***UMass Agreement***" means that certain Exclusive License Agreement between the University of Massachusetts and Ionis dated January 14, 2010, as amended.

"***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 seven years, not including in calculating such seven-year period of 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 [***] 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

[***]

APPENDIX 3

ASO Development Candidate Identification Plans

[***]

SCHEDULE 1.3.1

JSC GOVERNANCE

(a) The JSC will determine the JSC operating procedures, including frequency of meetings (at least quarterly), location of meetings, and responsibilities for agendas and minutes. The JSC will codify these operating procedures in the written minutes of the first meeting.

(b) The JSC may hold meetings in person or by audio or video conference as determined by the JSC; but at least two meetings per year will be in person (one held at Ionis' facilities, and the other held at Biogen's facilities in the U.S.). Alliance Managers will attend JSC meetings as participating non-members. In addition, upon prior approval of the other Party, each Party may invite its employees or consultants to attend JSC meetings, including any subject matter expert(s) with valuable knowledge of SMN2 or Spinal Muscular Atrophy.

(c) The co-chairs will be responsible for ensuring that activities occur as set forth in this Agreement, including ensuring that JSC meetings occur, JSC recommendations are properly reflected in the minutes, and any dispute is given prompt attention and resolved in accordance with Section 7.1.3 and Section 12.1, as applicable.

(d) The JSC members from the same Party will collectively have one vote. The JSC will strive to make recommendations with approval of both Ionis members and Biogen members, and record such recommendations in the minutes of the JSC meeting.

(e) The JSC 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 JSC dissolves.

SCHEDULE 1.3.5

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 Collaboration Programs;

(c) Organizing JSC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the JSC 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 JSC;

(f) Ensuring compliance in maintaining the Ionis Internal ASO Safety Database as outlined in Section 5.3; and

(g) Ensuring proper approval of publications prior to submission as required in Section 11.3.

SCHEDULE 1.5

List of [***]

For [***] studies:

[***]

For [***] studies:

[***]

SCHEDULE 4.9.2(C)

Ionis' Fully Absorbed Cost of Goods Methodology
Cost Estimate of API Cost per Kilogram
(OOO's)

[***]

SCHEDULE 5.1

Biogen's Development and Commercialization Activities

[***]

SCHEDULE 5.1.1

Integrated Development Plan Content

[***]

SCHEDULE 6.6.2(f)

Royalty Calculation Examples

[***]

SCHEDULE 6.6.2(g)

Allocation of Net Sales

[***]

SCHEDULE 6.8.1

Ionis In-License Agreements

(Relevant to the Compounds as of the Effective Date)

[***]

SCHEDULE 6.8.3(b)

Royalty Rate Reduction Example

[***]

SCHEDULE 8.2.6(a)

Ionis Core Technology Patents

[***]

SCHEDULE 8.2.6(b)

Ionis Manufacturing and Analytical Patents

[***]

SCHEDULE 8.2.6(c)

Ionis Product-Specific Patents

[***]

SCHEDULE 8.2.9

Prior Agreements

[***]

SCHEDULE 10.4.5(b)

Advisory Panel Regarding Setoff Disputes

[***]

SCHEDULE 10.4.6

Transition Services

[***]

SCHEDULE 12.1.2

Mediation

1. Mediation.

1.1. If a Dispute cannot be resolved pursuant to Section 12.1.1 of the Agreement (Escalation), the Parties agree to try in good faith to resolve any such Dispute by non-binding mediation administered by the American Arbitration Association (the "***AAA***") in accordance with its Commercial Mediation Procedures then in effect (the "***Procedures***"), as modified by this Section 1.1 of this SCHEDULE 12.1.2. The mediation will be conducted by a single mediator appointed by agreement of the Parties, within 15 days after either Party notifies the other Party of its intention to mediate such Dispute, or failing such agreement, appointed by the AAA in accordance with the Procedures; *provided*, that in either case the mediator will be a retired Delaware state or federal judge. Unless otherwise mutually agreed upon by the Parties, the mediation proceedings will be conducted in Dover, Delaware. The Parties agree that they will share equally the costs and expenses of the mediation; *provided*, that each Party will bear its own attorneys' fees and associated costs and expenses. The mediation conference will be held within [***] after appointment of the mediator, and will last no more than two consecutive days unless otherwise mutually agreed upon by the Parties. Any resolution of a Dispute by mediation pursuant to this Section 1.1 of these mediation procedures will be in writing and signed by duly authorized representatives of both Parties.

1.2. If the Parties cannot resolve a Dispute in accordance with Section 1.1 of this SCHEDULE 12.1.2, then such Dispute will be resolved by the Parties in accordance with Section 12.2 of the Agreement (Governing Law; Jurisdiction; Venue; Service of Process).

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 Securities Corporation, a Massachusetts Corporation

Akcea Therapeutics UK Limited, a United Kingdom Limited Private Company

Akcea Intl Ltd., a Cayman Islands Limited Liability 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

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, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777, 333-151996, 333-160269, 333-168674, 333-176136, 333-184788, 333-190408 and 333-207900) of Ionis Pharmaceuticals, Inc. of our reports dated February 28, 2018, 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, 2017.

/s/ ERNST & YOUNG LLP

San Diego, California
February 28, 2018

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, 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 28, 2018

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., 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 28, 2018

/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), Stanley T. Crooke, 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, 2017, 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 28, 2018

/s/ STANLEY T. CROOKE	/s/ ELIZABETH L. HOUGEN
Stanley T. Crooke, M.D., Ph.D.	Elizabeth L. Hougen
Chief Executive Officer	*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.