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, 2018

☐ **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 every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

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

Large accelerated filer ☒	Accelerated filer ☐
Non-accelerated filer ☐	Smaller reporting company ☐ Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 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 $4,805,287,142 as of June 30, 2018.*

The number of shares of voting common stock outstanding as of February 20, 2019 was 138,397,754.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 26, 2019 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 6, 2019 are incorporated by reference into Part III of this Report.

* Excludes 21,838,695 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, 2018. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

FORWARD-LOOKING STATEMENTS

This report on Form 10-K and the information incorporated herein by reference includes forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen) and our technologies and products in development, including the business of Akcea Therapeutics, Inc., our majority-owned affiliate. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing 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 Boston, Massachusetts. Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea's stock. At December 31, 2018, we owned approximately 75 percent of Akcea's stock.

IONIS PHARMACEUTICALS, INC.
FORM 10-K
For the Fiscal Year Ended December 31, 2018
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PART I

Item 1. Business

We are a leader in discovering and developing RNA-targeted therapeutics with sustained and growing revenues. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics that we believe has fundamentally changed medicine and transformed the lives of people with devastating and often deadly diseases. Our large, diverse and advanced pipeline of over 40 first-in-class and/or best-in-class medicines addresses diseases across a broad range of therapeutic areas, targeting small, medium and large patient populations.

We have two commercial medicines approved in major markets around the world, SPINRAZA and TEGSEDI. We have at least four medicines that have entered pivotal studies or have the potential to begin pivotal studies this year, and another six medicines that could start pivotal studies in 2020. These medicines, along with the more than 30 additional medicines in our pipeline, represent multiple potential drivers of value for years to come. We believe our efficient drug discovery platform, coupled with our innovation-centric business model, provides us with the flexibility to determine the optimal development and commercialization strategy to maximize the commercial opportunity for each of our medicines and ensure that we continue to produce transformative medicines for patients who need them. We believe we are positioned to drive substantial value for patients and shareholders.

As of January 2019, SPINRAZA was approved in over 40 countries around the world, and our partner Biogen, who is responsible for global SPINRAZA commercial activities, reported that more than 6,600 patients are now on SPINRAZA therapy. In addition, Biogen plans to continue to pursue regulatory filings in additional countries. Biogen reported 2018 annual sales of SPINRAZA of more than $1.7 billion, and we earned $238 million in commercial revenues from royalties on sales of SPINRAZA. SPINRAZA is the first and only approved medicine for the treatment of spinal muscular atrophy, or SMA. SPINRAZA is the established standard-of-care for all people with this progressive, debilitating and often fatal genetic disease. In November 2018, SPINRAZA was recognized with the 2018 International Prix Galien award as Best Biotechnology Product. This prestigious honor marks the seventh Prix Galien award for SPINRAZA.

TEGSEDI, a once weekly, self-administered subcutaneous medicine, was approved in 2018 in the U.S., EU and Canada for the treatment of polyneuropathy caused by hereditary TTR amyloidosis, or hATTR, in adult patients. hATTR is a debilitating, progressive, and fatal disease. Akcea, our majority-owned affiliate focused on developing and commercializing medicines to treat patients with rare and serious diseases, launched TEGSEDI globally in late 2018. In the fourth quarter of 2018, we earned more than $2 million in TEGSEDI product sales. Akcea has an exclusive license agreement with PTC Therapeutics, or PTC, to commercialize TEGSEDI in Latin America. In January 2019, PTC filed an application for regulatory approval in Brazil with ANVISA, the Brazilian regulatory authority. ANVISA granted priority review for TEGSEDI.

We and Akcea are preparing to commercialize WAYLIVRA in the EU. The Committee for Medicinal Products for Human Use, or CHMP, of the European Medicines Agency, or EMA, adopted a positive opinion recommending conditional marketing authorization for WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion will now be referred to the European Commission, or EC, which grants marketing authorization for medicines in the EU, as well as to European Economic Area members Iceland, Liechtenstein and Norway. With this positive opinion, and, pending adoption of the positive opinion by the EC, Akcea plans to leverage its existing commercial infrastructure in Europe to market WAYLIVRA. Akcea is continuing to conduct open-label extension and early access programs. We are also focused on regulatory discussions in the U.S. We are developing WAYLIVRA to treat familial partial lipodystrophy, or FPL, a second severe and rare, genetically defined disease. 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.

In addition to commercializing TEGSEDI and preparing to commercialize WAYLIVRA, Akcea is developing four other clinical-stage medicines: AKCEA-APO(a)-L_{Rx} (TQJ230), AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-TTR-L_{Rx}, each of which could potentially treat multiple patient populations. Moving these drugs into Akcea allows us to retain substantial value from these medicines and ensures our core focus remains on innovation. As of February 2019, we owned approximately 75 percent of Akcea.

We are continuously advancing our technology and pipeline to provide the most value to patients. We have a pipeline of over 40 medicines that, like SPINRAZA and TEGSEDI, have the potential to transform the treatment of diseases with no adequate treatment today. These medicines range from treatments for rare diseases with small patient populations to more common diseases afflicting millions of patients. Our pipeline covers a broad spectrum of therapeutic areas, such as cardiometabolic diseases, neurodegenerative diseases, cancer, severe and rare diseases and others. We believe our large and diverse pipeline contains many near-, mid- and longer-term growth drivers for the company.

Our pipeline includes at least 10 potentially transformative medicines anticipated to enter pivotal clinical studies in the next two years. We anticipate at least four of these medicines will enter pivotal studies this year including: AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, IONIS-HTT_{Rx} (RG6042) and IONIS-$SOD1_{Rx}$. Roche recently initiated a Phase 3 study of IONIS-HTT_{Rx} for Huntington's disease, or HD. We believe each of these medicines is a first-in-class and/or best-in-class medicine with the potential to deliver significant value to patients and shareholders. We anticipate that the data from these pivotal studies, if positive, will support global regulatory filings for each medicine.

AKCEA-APO(a)-L$_{Rx}$ (TQJ230) – In February 2019, Novartis exercised its option to license AKCEA-APO(a)-L_{Rx} and we earned a $150 million license fee. Novartis is responsible for conducting and funding all future development and commercialization activities for AKCEA-APO(a)-L_{Rx}, including a global pivotal cardiovascular outcomes study, for which planning and initiation activities are underway. AKCEA-APO(a)-L_{Rx} targets a cardiovascular risk factor, lipoprotein(a) or Lp(a). Lp(a) is well-recognized by the medical community as a major risk factor for cardiovascular disease. Lp(a) is genetically determined at birth and there are currently no treatments available to substantially and specifically lower Lp(a). In September 2018, we reported dose-dependent and substantial reductions in Lp(a) levels in the Phase 2 clinical study in patients with established cardiovascular disease, or CVD, due to elevated levels of Lp(a), which was also the longest and largest study, regardless of phase, conducted with a LICA antisense medicine to date. Approximately 98 percent of patients who received the highest dose in the study demonstrated a reduction in Lp(a) levels to below 50 mg/dL, the recognized threshold for risk of CVD. In addition, AKCEA-APO(a)-L_{Rx} demonstrated a favorable safety and tolerability profile in the study.

AKCEA-TTR-L$_{Rx}$ – We are developing AKCEA-TTR-L$_{Rx}$ for the treatment of people with all forms of TTR amyloidosis as a once a month or even less frequent subcutaneous self-administered injection. In April 2018, we licensed to Akcea the worldwide rights to commercialize TEGSEDI and AKCEA-TTR-L$_{Rx}$. We plan to report data from the Phase 1/2 study this year, followed by the initiation of a pivotal program. We plan to initiate a Phase 3 study in patients with hereditary TTR amyloidosis with polyneuropathy first, followed closely by a Phase 3 study in patients with wild type and hereditary TTR cardiomyopathy, also planned for this year.

IONIS-HTT$_{Rx}$ (RG6042) – Roche initiated the Phase 3 study of IONIS-HTT$_{Rx}$ for HD in December 2018 and we earned a $35 million milestone payment when the first patient was dosed in the Phase 3 study in January 2019. HD is a genetic, devastating and fatal neurodegenerative disease that negatively affects psychological, cognitive and motor functions. In March 2018, we reported data from a Phase 1/2 study that demonstrated up to a 60 percent reduction in the mutant huntingtin protein, or mHTT, as observed in the cerebral spinal fluid, or CSF. It was the first study to demonstrate disease-modifying potential in HD patients. Based on preclinical data, the mHTT reductions of 40-60 percent in the CSF are predicted to result in 55-85 percent reduction in the cortex of the brain, where mHTT is highly expressed. IONIS-HTT$_{Rx}$ demonstrated a favorable safety and tolerability profile in the study.

IONIS-SOD1$_{Rx}$ (BIIB067) – IONIS-SOD1$_{Rx}$, for people with amyotrophic lateral sclerosis, or ALS, is the fourth medicine we anticipate we will move into pivotal studies this year. ALS is a rare, fatal neurodegenerative disease characterized by the loss of motor neurons in the brain and spinal cord resulting in an inability to control muscle movement. Scientists have identified mutations within multiple genes as causative of ALS, including mutations in the SOD1 gene. IONIS-SOD1$_{Rx}$ directly targets the SOD1 gene and is delivered intrathecally into the CSF. The average life expectancy for an ALS patient with the SOD1 mutation is less than five years from the time of diagnosis. Based on the positive interim analysis from the Phase 1/2 study that demonstrated proof-of-biology and proof-of-concept, in December 2018, Biogen exercised its licensing option with us to develop and commercialize IONIS-SOD1$_{Rx}$. IONIS-SOD1$_{Rx}$ demonstrated a favorable safety and tolerability profile in the study. Biogen plans to add an additional cohort to this study to potentially support registration. We earned $40 million in payments from Biogen in the fourth quarter of 2018 when Biogen advanced and licensed IONIS-SOD1$_{Rx}$.

The depth of our knowledge and expertise with antisense technology together with our strong financial position provides us the flexibility to partner our medicines at what we believe is the optimal time to maximize the near-term, mid-term and long-term value of our medicines. We have a distinct partnering strategy based on each specific medicine and the expertise and resources we and our potential partners may bring to a collaboration. We may develop and commercialize some medicines through affiliates. In general, these are medicines, like TEGSEDI, that can benefit from our internal expertise and infrastructure, have manageable development costs and have the potential for initial rare disease indications. For other medicines, we may establish collaborations to advance the medicine. We have alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our medicines, advancing our technology, preparing to commercialize our medicines and selling our medicines. Our partners include the following companies, among others: AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis and Roche. Our partners bring resources and expertise that augment and build upon our internal capabilities. For example, we partnered AKCEA-APO(a)-L$_{Rx}$ with Novartis because we believe Novartis brings significant resources and expertise that should accelerate our ability to deliver AKCEA-APO(a)-L$_{Rx}$ to the large population of patients with elevated levels of Lp(a) and established CVD. As a result of Novartis exercising its option for AKCEA-APO(a)-L$_{Rx}$ in February 2019, Novartis is responsible for conducting and funding all future development and commercialization activities, including a Phase 3 cardiovascular outcomes study Novartis is planning to conduct. We are eligible to earn additional payments from Novartis as AKCEA-APO(a)-L$_{Rx}$ progresses.

We are now a multi-product commercial company. 2018 marks our seventh consecutive year of revenue growth. Through our partnerships, we have earned significant commercial revenue and 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 investing in advancing our pipeline and technology. Moreover, we have the potential to earn over $20 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. Looking forward, we believe we have the potential to increase our commercial revenue from SPINRAZA royalties and TEGSEDI product sales from the continued growth we anticipate in the U.S., EU and other markets globally. We also have the potential to further increase our commercial revenue with the potential approval of WAYLIVRA.

We ended 2018 with a strong balance sheet with more than $2 billion in cash and short-term investments, making this the sixth year out of seven that we have been cash accretive. Our strong balance sheet provides us with the financial wherewithal to invest in expanding and advancing our pipeline, in commercializing our medicines through commercial affiliates, and advancing our technology.

Our Marketed Medicines – Transformational Medicines Bringing Value to Patients Today

SPINRAZA – SPINRAZA (nusinersen) injection for intrathecal use is a survival motor neuron-2, or SMN2, directed antisense oligonucleotide indicated for the treatment of SMA in pediatric and adult patients. SPINRAZA is the first and only approved medicine for the treatment of SMA and is the established standard-of-care for all people around the globe with this progressive, debilitating genetic disease. SPINRAZA is approved in over 40 countries around the world. In February 2019, SPINRAZA was approved by the China National Medical Products Association. Our partner, Biogen, who is responsible for global SPINRAZA commercial activities, reported in January 2019 that approximately 6,600 patients were on SPINRAZA therapy. Biogen reported 2018 annual sales of more than $1.7 billion, and we earned $238 million in commercial revenues from royalties on sales of SPINRAZA.

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, or Type 1, SMA, can become paralyzed and have difficulty performing the basic functions of life, like breathing and swallowing. Due to a loss of, or defect in, the SMN1 gene, people with SMA do not produce enough 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 Type 1 SMA produce very little SMN protein and do not achieve the ability to sit without support or live beyond two years without respiratory support. Patients with later-onset, or Type 2 or Type 3 SMA, produce greater amounts of SMN protein and have less severe, but still life-altering, forms of SMA.

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

Biogen is conducting NURTURE, a Phase 2 open-label study of SPINRAZA in pre-symptomatic infants. Biogen presented an interim analysis of the NURTURE data at the Annual Congress of the World Muscle Society in October 2018. The interim analysis showed that SPINRAZA-treated infants achieved motor milestones in timelines more consistent with normal development than what is observed in the natural history of patients with Type 1 SMA. At the time of the interim analysis, all patients were alive and did not require respiratory intervention. All of the infants in the study were able to sit without support and 88 percent of the infants were able to walk either with assistance or independently. No new safety concerns were identified.

The safety and efficacy of SPINRAZA has been evaluated in 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.

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, sit, and stand. Additionally, infants treated with SPINRAZA demonstrated a statistically significant improvement in event-free survival compared to untreated patients.

In the CHERISH EOS 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. The majority of children treated with SPINRAZA demonstrated benefits in upper limb and general motor function, including crawling and standing with support. The overall findings from the CHERISH EOS analysis continue to support the robust efficacy and favorable safety profile of SPINRAZA across a broad patient population.

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 (Any information that is included on or linked to this website is not part of this report or any registration statement or report that incorporates this report by reference).

TEGSEDI – TEGSEDI (inotersen) injection is a Generation 2+ antisense medicine and the world's first and only approved subcutaneous RNA-targeting medicine designed to treat people with polyneuropathy caused by hATTR. In October 2018, the FDA approved TEGSEDI for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. TEGSEDI is also approved in the EU and Canada for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis. It is administered as a once weekly, self-administered, at-home, subcutaneous injection. In March 2018, Akcea licensed TEGSEDI from us.

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

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

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

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

Thrombocytopenia and safety signals related to renal function were identified during the study. 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.

Additionally, at the 60th American Society of Hematology, or ASH, Annual Meeting and Exposition held in December 2018, we presented data from the open-label extension study, or OLE, in patients with hATTR treated with TEGSEDI. The OLE is an ongoing study and is intended to evaluate the long-term efficacy and safety profile of TEGSEDI. The benefits observed from TEGSEDI in the NEURO-TTR study continued in the OLE. In addition, the OLE results demonstrated that patients who initiated TEGSEDI treatment at the start of the NEURO-TTR study, 15 months earlier, experienced greater benefit than those who received placebo treatment in the NEURO-TTR study and then initiated treatment in the OLE. Patients who began the NEURO-TTR study on placebo experienced a rapid onset of effect following TEGSEDI treatment that has been sustained for up to 2 years in the OLE. These patients further experienced improvements in quality of life and activities of daily living as measured by Norfolk QoL-DN and showed improved mNIS+7 progression compared to their rate of progression in the NEURO-TTR study. Specifically, these patients experienced a mean increase in Norfolk QoL-DN of 16.8, a 10 point improvement over projected placebo values and a mean increase in mNIS+7 of 34 points from baseline, a 24 point improvement over projected placebo values. No new safety concerns were identified in the OLE.

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

We developed TEGSEDI under a collaboration agreement we had with GSK. Under the agreement, we are required to pay GSK a nominal royalty on net sales of TEGSEDI.

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

Drug Discovery and Development

Introduction to Drug Discovery

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

Our Development Projects

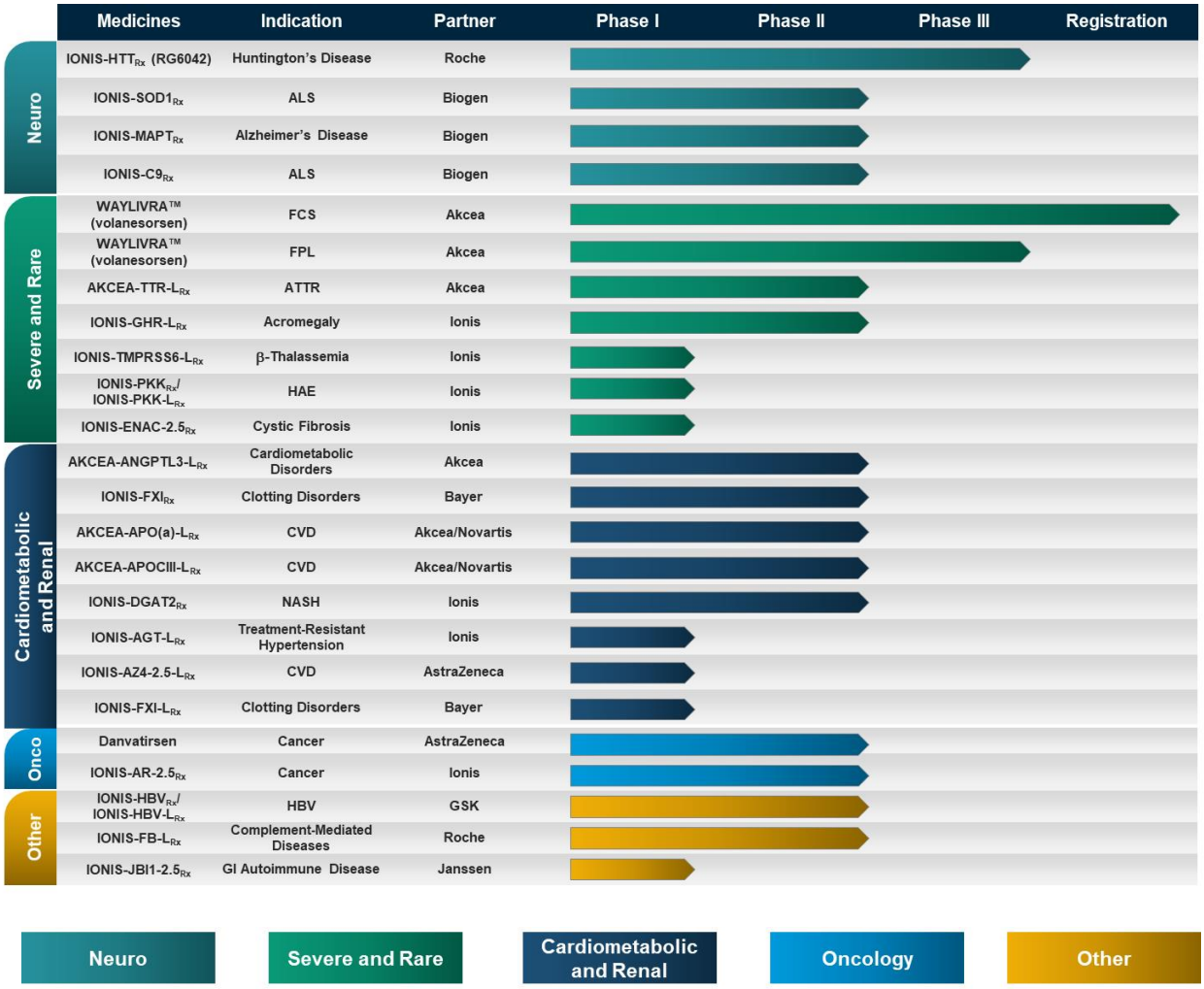
We are a leader in the discovery and development of an exciting class of RNA-targeted medicines called antisense oligonucleotide, or ASO, medicines, or just antisense medicines. With our proprietary drug discovery platform, we can rapidly identify medicines from a wealth of potential targets to treat a broad range of diseases. We focus our efforts in therapeutic areas in which our medicines will work best, efficiently screening many targets in parallel and carefully selecting the best candidates. By combining this efficiency with our rational approach to selecting disease targets, we have built a large and diverse portfolio of medicines we designed to treat a variety of health conditions, such as cardiometabolic diseases, neurodegenerative diseases, cancer, severe and rare diseases and others. We are developing antisense medicines for systemic and local delivery (e.g., intrathecal, intraocular, oral and aerosol).

We plan to continue to add new medicines to our pipeline, building a broad proprietary portfolio of medicines to treat many diseases and creating opportunities to generate substantial revenue. We also continue to improve our scientific understanding of our medicines, including how our medicines impact the biological processes of the diseases we target.

With our expertise in discovering and characterizing novel antisense medicines, our scientists can optimize the properties of our antisense medicines against each particular target. Our scientists have made significant advances in chemical modifications we use in our antisense medicines, such as with our Generation 2+ antisense medicines, which have increased potency and an improved side effect profile over our earlier generation medicines. Our scientists have further improved upon our second-generation chemistry with our Generation 2.5 chemistry, an advancement that further increases the potency of our medicines, which broadens the organs and tissues in which our medicines can work. We currently have 13 Generation 2.5 medicines in development, and we anticipate that more of our future medicines will incorporate our Generation 2.5 chemistry.

In addition to improving the chemical foundation of our medicines, we have also created LIgand-Conjugated Antisense, or LICA, technology, which we design to enhance the effective uptake and activity of our medicines in particular tissues. With our LICA technology we attach specific chemical structures or molecules to our antisense medicines. With our first LICA conjugate, a complex sugar-like molecule called N-acetylgalactosamine, or GalNac, we have shown an increase in medicinal potency of over 30-fold for liver targets, compared to non-conjugated antisense medicines. We currently have 13 LICA medicines in development, including two medicines that combine our Generation 2.5 chemistry and LICA technology.

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



The above table lists the medicines in our pipeline that are in registration for marketing authorization or in clinical trials. The table includes the disease indication, a partner (if the medicine is partnered), and the development status of each medicine. Typically, the names of our medicines incorporate the target of the medicine. For example, with IONIS-HTT$_{Rx}$, the RNA produced from the huntingtin gene, represented by the acronym HTT, is the target of the medicine. Unless indicated otherwise, the majority of medicines in our pipeline are Generation 2+ antisense medicines. We differentiate medicines discovered at Ionis but being developed by Akcea by using "AKCEA", instead of "IONIS" at the beginning of the medicine name, such as AKCEA-ANGPTL3-L$_{Rx}$. We differentiate our Generation 2.5 medicines by adding a "2.5" notation at the end of the medicine name, such as IONIS-JBI1-2.5$_{Rx}$. We differentiate our LICA medicines by adding an "L" at the end of the medicine name, such as IONIS-PKK-L$_{Rx}$. As the medicines in our pipeline advance in clinical development, we will adopt nonproprietary names given to each medicine from the U.S. Adopted Names Council. For example, inotersen is a nonproprietary name that we obtained for IONIS-TTR$_{Rx}$. Once we or our partners establish a brand name, we will adopt the brand name. For example, TEGSEDI is the brand name for inotersen.

With a pipeline as large and advanced as ours, we have a number of clinical events each year as we initiate new clinical studies, complete and report data from clinical studies, and add numerous new medicines to our pipeline.

WAYLIVRA – Potential Approval in Europe Following Positive CHMP Opinion

WAYLIVRA (volanesorsen) – WAYLIVRA is a Generation 2+ antisense medicine we and Akcea 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. We are preparing to commercialize WAYLIVRA in the EU.

In February 2019, the CHMP of the EMA adopted a positive opinion recommending conditional marketing authorization for WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion will now be referred to the EC, which grants marketing authorization for medicines in the EU, as well as to European Economic Area members Iceland, Liechtenstein and Norway. With this positive opinion, and, pending adoption of the positive opinion by the EC, Akcea plans to leverage its existing commercial infrastructure in Europe to market WAYLIVRA.

In August 2018, we received a complete response letter, or CRL, from the Division of Metabolism and Endocrinology Products of the FDA regarding the NDA for WAYLIVRA. We are continuing our discussions with the FDA regarding WAYLIVRA.

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. It is estimated to affect 3,000 to 5,000 people in treatable markets. In addition, people with FCS must adhere to a very strict, low-fat diet. FPL is a rare, orphan disease that is estimated to affect 3,000 to 5,000 patients worldwide. Patients with FPL typically have diabetes and other metabolic abnormalities, including elevated triglycerides, which increases their risk of pancreatitis. As a result of these factors, people with FCS and FPL are often unable to work, adding to the burden of these diseases. In severe cases, patients can have bleeding into the pancreas, serious tissue damage, infection and cyst formation, as well as damage to other vital organs such as the heart, lungs and kidneys.

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

The marketing authorization application for WAYLIVRA is based on results from the Phase 3 APPROACH study and the ongoing APPROACH Open Label Extension, or OLE, study and supported by results from the Phase 3 COMPASS study. 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 WAYLIVRA-treated patients. We observed 50 percent of treated patients achieved triglyceride levels below 500 mg/dL, a commonly accepted threshold for pancreatitis risk. In addition, in the APPROACH study, treatment with WAYLIVRA was associated with a statistically significant reduced rate of pancreatitis attacks in the group of patients who had the highest incidence of pre-study pancreatitis and reduced abdominal pain in patients reporting pain before treatment in the study.

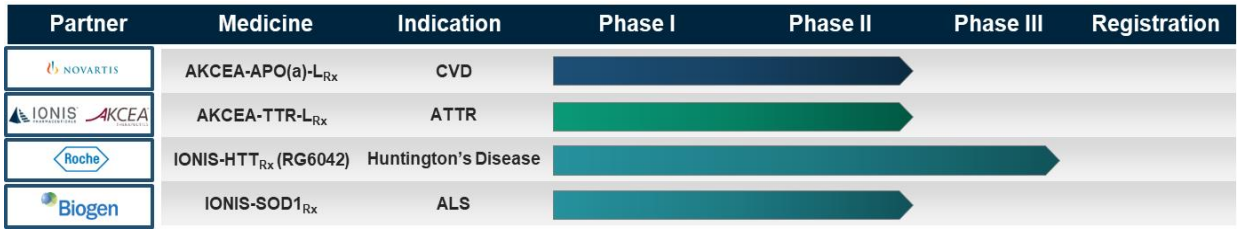
The most common adverse event in the studies was injection site reactions, which were mostly mild. In addition, declines in platelet counts were observed in many patients and some patients discontinued the study because of platelet declines. These platelet declines were not clinically significant in 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. 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 WAYLIVRA was associated with a statistically significant reduction in on-study pancreatitis attacks. The most common adverse event in the WAYLIVRA-treated group of patients was injection site reactions, which were mostly mild. In addition, a potentially treatment-related SAE of serum sickness reaction, from which the patient fully recovered, was reported. There have been no deaths and no treatment-related bleeding or cardiovascular events in any WAYLIVRA clinical study.

We are conducting the BROADEN study, a Phase 3 clinical trial in patients with FPL, with data anticipated this year.

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. Additionally, we have expanded access programs, or EAPs, for WAYLIVRA. Patients in the BROADEN study are also eligible to roll over into an open-label extension study upon completing dosing in the pivotal study. We plan to commercialize WAYLIVRA through Akcea for patients with FCS and FPL, if approved in other markets.

Potential Next Wave of Pivotal Medicines

Focusing on our key fundamental strategies has created a deep and broad pipeline of over 40 first-in-class and/or best-in-class medicines that we believe have the potential to deliver significant value to patients affected by these devastating diseases, many of which have limited treatment options. We have at least four medicines that have begun pivotal studies or have the potential to begin pivotal studies this year.



AKCEA-APO(a)-LRx (TQJ230) – AKCEA-APO(a)-L_{Rx} is a Generation 2+ LICA medicine 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 50 mg/dL.

Lp(a) is difficult to inhibit using other technologies, such as small molecules and antibodies. There are multiple genetically-determined forms of the Apo(a) molecule and creating a small molecule or antibody that can interact with multiple targets is difficult. We believe antisense technology is well suited to address hyperlipoproteinemia(a) because antisense technology specifically targets the RNA that codes for all forms of the Apo(a) molecule. 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.

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

In February 2019, Novartis exercised its option to license AKCEA-APO(a)-L_{Rx} and Novartis' preparations to initiate Phase 3 a cardiovascular outcomes study are already underway

AKCEA-TTR-LRx – We are co-developing AKCEA-TTR-L_{Rx} with Akcea to inhibit the production of transthyretin, the same protein inhibited by TEGSEDI (inotersen). There are two types of ATTR amyloidosis: hATTR amyloidosis and wt-ATTR amyloidosis.

We are developing AKCEA-TTR-L_{Rx} for the treatment of people with all forms of TTR amyloidosis as a once a month or even less frequent subcutaneous self-administered injection. We plan to report data from the Phase 1/2 study this year, followed by the initiation of a pivotal program. We plan to initiate a Phase 3 study in patients with hereditary TTR amyloidosis with polyneuropathy first, followed closely by a Phase 3 study in patients with wild type and hereditary TTR cardiomyopathy, also planned for this year.

IONIS-HTTRx – IONIS-HTT_{Rx} (RG6042) is a Generation 2+ antisense medicine we designed to target the underlying cause of HD by reducing the production of the toxic mHTT protein. Roche initiated the Phase 3 study of IONIS-HTT_{Rx} for Huntington's disease, or HD, in December 2018 and the first patient was dosed in the Phase 3 study in January 2019. In addition to the Phase 3 study, all participants who took part in the Phase 1/2 study are eligible to continue to receive IONIS-HTT_{Rx} as part of an OLE study to assess the safety and tolerability of IONIS-HTT_{Rx}. In parallel with the Phase 3 study and the OLE, Roche initiated a natural history study in a similar patient population to the OLE. The natural history study is planned as a 15-month observational study aimed at further understanding the role of mHTT in disease progression and is anticipated to include up to 100 participants with Stage I and II HD. There is no drug treatment in the observational study, as the goal is to understand the natural progression of HD.

We completed a randomized, placebo-controlled, dose escalation, Phase 1/2 clinical study of IONIS-HTT_{Rx} in patients with early stage HD. In this study, we observed dose-dependent reductions of mHTT among patients treated with IONIS-HTT_{Rx} and IONIS-HTT_{Rx} demonstrated a favorable safety and tolerability profile. In March 2018, we reported data from the study that demonstrated up to a 60 percent reduction in the mHTT as observed in the CSF. It was the first study to demonstrate disease-modifying potential. The mHTT reductions of 40-60 percent in the CSF correspond to an estimated 55-85 percent reduction in the cortex of the brain, where mHTT is highly expressed, based on preclinical data. There were no serious adverse events reported and no participants discontinued from the study. In August 2018, the EMA granted PRIME designation to IONIS-HTT_{Rx}. EMA PRIME status is granted to medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. The FDA and EMA granted Orphan Medicine Designation for IONIS-HTT_{Rx} to treat people with HD.

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 are no disease-modifying treatments available for HD patients, with current drugs only managing some disease symptoms.

We entered into a collaboration with Roche to develop and commercialize antisense medicines to treat HD in April 2013. In December 2017, Roche exercised its licensing option to develop and commercialize IONIS-HTT_{Rx} following the completion of a Phase 1/2 randomized, placebo-controlled, dose escalation study of IONIS-HTT_{Rx} in people with HD. Roche is responsible for all IONIS-HTT_{Rx} development, regulatory and commercialization activities and costs.

IONIS-SOD1Rx (BIIB067) – IONIS-$SOD1_{Rx}$ is a Generation 2+ antisense medicine we designed to reduce the production of superoxide dismutase 1, or SOD1, which is a well 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 breathing and swallowing and eventually succumb to the disease. Currently, treatment options for people with ALS are extremely limited, with no medicines that significantly slow disease progression.

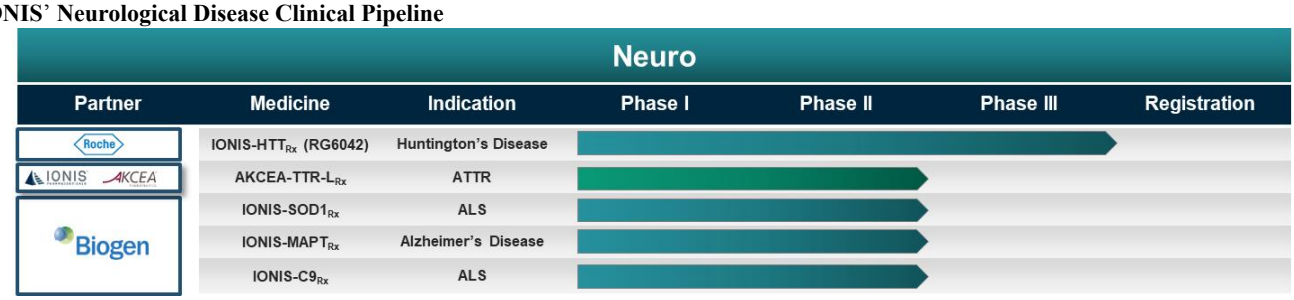
In December 2018, Biogen exercised its licensing option to develop and commercialize IONIS-$SOD1_{Rx}$ based on the positive interim analysis from the Phase 1/2 study that demonstrated proof-of-biology and proof-of-concept. Biogen is responsible for all IONIS-$SOD1_{Rx}$ development, regulatory and commercialization activities and costs. At the highest dose tested, treatment with IONIS-$SOD1_{Rx}$ over a three month period resulted in a statistically significant lowering of SOD1 protein levels in the CSF and positive numerical trends across three efficacy endpoints: slowing of clinical decline as measured by the ALS functional rating scale-revised, slowing of decline in respiratory function as measured by vital capacity and slowing of decline in muscle strength as measured by a handheld device, all compared to placebo. The safety and tolerability profile in this study supports the continued development of IONIS-$SOD1_{Rx}$ in ALS.

Biogen plans to add an additional cohort to this study to potentially support registration of IONIS-$SOD1_{Rx}$.

Neurological Disease Franchise

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

IONIS' Neurological Disease Clinical Pipeline



IONIS-HTTRx – See the medicine description under "Next Wave of Pivotal Medicines" section above.

AKCEA-TTR-LRx – See the medicine description under "Next Wave of Pivotal Medicines" section above.

IONIS-SOD1Rx – See the medicine description under "Next Wave of Pivotal Medicines" section above.

IONIS-MAPTRx – IONIS-$MAPT_{Rx}$ is a Generation 2+ antisense medicine we 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, common forms of dementia.

Microtubule-associated protein tau, or tau, is a contributor or cause of certain neurodegenerative diseases, known as tauopathies, characterized by the deposition of abnormal tau protein in neurons and non-neuronal cells in the brain. AD and FTD are characterized by predominant memory impairment and behavioral changes, resulting in a person's inability to independently perform daily activities. AD generally occurs late in life and may progress to death in five to 20 years after the onset of the disease. FTD has a more rapid disease progression. There are approximately five million people living with AD in the U.S. and approximately 55,000 people affected by FTD in the U.S.

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

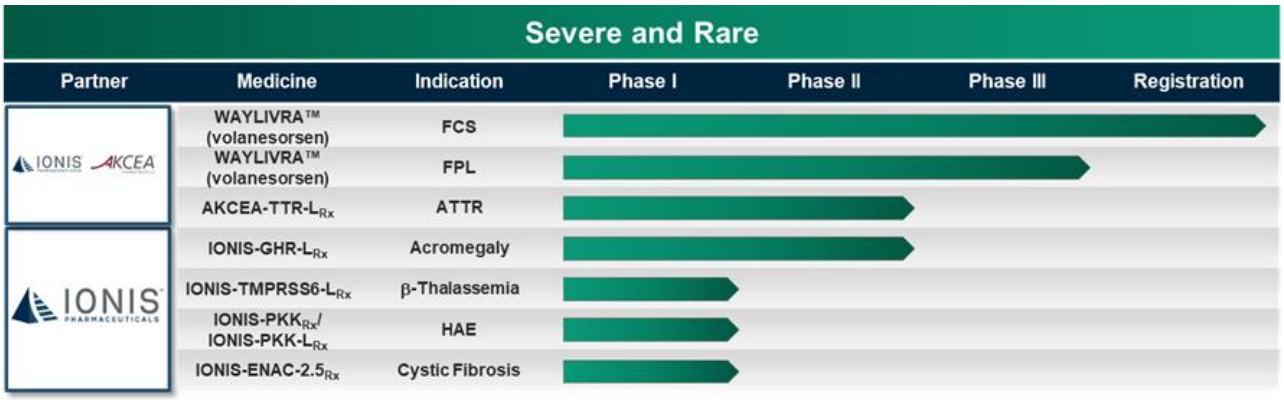
IONIS-C9Rx – IONIS-C9$_{Rx}$, also referred to as BIIB078, is a Generation 2+ antisense medicine we designed to selectively reduce the production of the mutated chromosome 9 open reading frame 72, or C9ORF72, gene. A mutation in this gene results in an inherited form of ALS, referred to as C9ORF72-ALS, the most prevalent genetic cause of ALS worldwide. There is substantial evidence that this mutation is responsible for a toxic gain of function repeat expansion that can lead to rapid progressive loss of motor neurons in people with C9ORF72-ALS. This is a fatal disease characterized by muscle weakness, loss of movement, and difficulty breathing and swallowing. We believe IONIS-C9$_{Rx}$ represents a novel approach to targeting ALS, for which there is no cure.

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

Severe and Rare Disease Franchise

Our severe and rare disease franchise is one the largest franchises in our pipeline. We are discovering and developing antisense medicines 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 7,000 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. For example, SPINRAZA was approved five years after we began the Phase 1 study for it.

IONIS' Severe and Rare Disease Clinical Pipeline



WAYLIVRA - See the medicine description under "WAYLIVRA - Under Regulatory Review for Marketing Authorization" section above.

AKCEA-TTR-LRx – See the medicine description "Next Wave of Pivotal Medicines" section above.

IONIS-GHR-LRx – IONIS-GHR-L$_{Rx}$ is a Generation 2+ LICA medicine 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, and life-threatening disease.

High levels of circulating GH and IGF-1 lead to this multisystem disease characterized by organ overgrowth and physical disfigurement, such as enlarged hands, feet, and facial features. Patients with acromegaly also experience multiple co-morbidities, such as type 2 diabetes, hypertension, and respiratory complications, as well as premature mortality. Because IGF-1 mediates the majority of the growth-promoting action of GH, reducing GHr production could in turn decrease levels of IGF-1 and provide a potential treatment to patients with acromegaly. Acromegaly is a rare disease with an estimated 25,000 patients in the U.S. Current treatments to block IGF-1 include surgical removal of the pituitary gland, which is often unsuccessful. Drug treatments to normalize IGF-1 levels are also available but are associated with potentially serious side effects.

We have completed a Phase 1, double-blind, placebo-controlled, dose-escalation study of IONIS-GHR-L_{Rx} in healthy volunteers. In this study, IONIS-GHR-L_{Rx} demonstrated a favorable safety and tolerability profile. There were no reports of deaths, serious adverse events or adverse events that led to study discontinuation. IONIS-GHR-L_{Rx} has the potential to bring substantial benefit to patients with acromegaly with at home, monthly subcutaneous administration.

In November 2018, we initiated the Phase 2 proof of concept clinical study of IONIS-GHR-L_{Rx} in acromegaly patients. The study is a randomized, double-blind, placebo-controlled, multi-center study in acromegaly patients uncontrolled on select long-acting somatostatin receptor ligands. Patients in the study will receive monthly subcutaneous injections for four months. We anticipate we will complete this study by the end of this year.

IONIS-TMPRSS6-LRx – IONIS-TMPRSS6-L_{Rx} is a Generation 2+ LICA medicine 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 is important in the regulation of the body's iron homeostasis through the control of the iron regulatory protein hepcidin. Inhibition of TMPRSS6 leads to increased production of hepcidin, which results in more effective red blood cell production in the bone marrow and reduced iron toxicity in the liver as a result of improved control of iron availability.

Patients with β-thalassemia can experience severe anemia, marrow expansion, bone deformities, as well as iron toxicity. While the severity of anemia varies between patients, iron toxicity is a common complication leading to high rates of mortality as a result of iron accumulation in major organs, such as the heart and liver. Currently there are no effective therapies for patients with β-thalassemia. The current standard of care is managing patients' symptoms with blood transfusions, hydroxyurea, and iron chelation.

β-thalassemia can be further subdivided into patients with transfusion-dependent thalassemia, or TDT, and non-transfusion dependent thalassemia, or NTDT, including β-thalassemia intermedia. Although transfusions are not needed to support life in patients with NTDT, the associated complications of the disease are severe and often fatal. There are approximately 20,000 people in North America and Europe who suffer from β-thalassemia intermedia.

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. In December 2018, we presented positive Phase 1 data at the ASH Annual Meeting. In a randomized, double-blind, placebo-controlled, dose-escalation Phase 1 study in healthy volunteers, we demonstrated dose-dependent reductions of serum iron and serum transferrin saturation. Additionally, we observed an increase in serum hepcidin and predicted changes in hemoglobin. IONIS-TMPRSS6-L_{Rx} demonstrated a favorable safety and tolerability profile.

We are planning to begin the Phase 2 proof of concept study of IONIS-TMPRSS6-L_{Rx} this year.

IONIS-PKKRx and IONIS-PKK-LRx – IONIS-PKK_{Rx} and IONIS-PKK-L_{Rx} are antisense medicines we designed to reduce the production of prekallikrein, or PKK, to treat people with hereditary angioedema, or HAE. It is a rare genetic disease that is characterized by rapid and painful attacks of inflammation in the hands, feet, limbs, face, abdomen, larynx and trachea and can be fatal if swelling occurs in the larynx. PKK plays an important role in the activation of inflammatory mediators associated with acute attacks of HAE. By inhibiting the production of PKK, IONIS-PKK_{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.

We have completed a Phase 1 study evaluating IONIS-PKK_{Rx} in healthy volunteers and we are exploring potential development options. In this study, IONIS-PKK_{Rx} demonstrated a favorable safety and tolerability profile. 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.

IONIS-ENAC-2.5Rx – IONIS-ENAC-2.5_{Rx} is a Generation 2.5 antisense medicine we designed to selectively reduce epithelial sodium channel, or EnaC, to treat people with cystic fibrosis, or CF. CF is an autosomal recessive disorder caused by mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator, or CFTR. CFTR is a chloride channel expressed in epithelial cells, including those in the lung. Targeting ENAC may enable treatment of all forms of CF due to various CFTR mutations, unlike existing therapeutics. CF is a multisystem disease that mostly affects the lungs, clogging airways due to mucus build-up and resulting in inflammation and infection. This disease is characterized by a progressive decline in lung function with acute periods of worsened symptoms, known as pulmonary exacerbations. CF is estimated to affect approximately 30,000 people in the U.S. and another 70,000 worldwide. Despite progress with other treatments, there remains a need for effective treatment options.

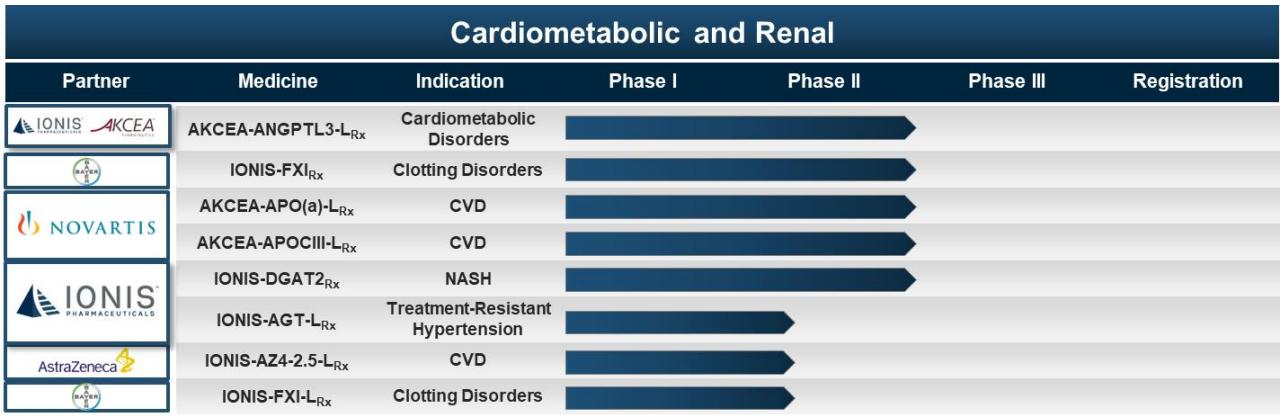
Antisense aerosol technology for lung delivery may provide a novel solution for targeting ENaC potentially enabling all patients with CF to be treated. In preclinical studies in transgenic rodents, treatment with ENaC-targeting antisense drugs specifically suppressed ENaC expression, resulting in the reduction of markers of CF mucus pathology and improved lung function. Treatment prevented manifestations of the disease from occurring and reversed existing CF.

In December 2018, we initiated a Phase 1 study of healthy volunteers in a double-blinded, placebo-controlled, dose-escalation study to evaluate the safety and efficacy of IONIS-ENAC-2.5_{Rx}. The study will consist of four randomized single-dose cohorts and four multiple-dose cohorts.

Cardiometabolic and Renal Disease Franchise

Cardiovascular disease is an important area of focus for us. According to the World Health Organization, or WHO, cardiovascular disease was the number one cause of death globally. An estimated 17.9 million people died from CVD in 2016, representing 31 percent of all deaths globally. The medicines 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 tens of 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 30 million people in the U.S., or nine percent of the population, with type 2 diabetes constituting 90 percent of those cases.

IONIS' Cardiometabolic and Renal Disease Clinical Pipeline



AKCEA-ANGPTL3-LRx – AKCEA-ANGPTL3-L_{Rx} is a Generation 2+ LICA medicine we designed to reduce the production of the angiopoietin-like 3, or ANGPTL3, protein. We and Akcea are developing AKCEA-ANGPTL3-L_{Rx} to treat nonalcoholic fatty liver disease, or NAFLD.

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 have completed a Phase 1/2 program for AKCEA-ANGPTL3-L_{Rx} in healthy volunteers with elevated triglycerides. Results for the initial cohort from this study were reported at the AHA meeting in November 2016 and the data were published in *The New England Journal of Medicine*. We observed that the people with elevated triglycerides achieved dose-dependent, statistically significant mean reductions in ANGPTL3 of up to 83 percent. Treatment with AKCEA-ANGPTL3-L_{Rx} was also associated with statistically significant mean reductions in triglycerides of up to 66 percent, in LDL-C of up to 35 percent and in total cholesterol of up to 36 percent. In this study, AKCEA-ANGPTL3-L_{Rx} demonstrated a favorable safety and tolerability profile.

In the fourth quarter of 2017, we initiated a multicenter, randomized, double-blind, placebo-controlled dose-ranging study of AKCEA-ANGPTL3-L_{Rx} in patients with NAFLD with metabolic complications, which include hypertriglyceridemia, type 2 diabetes and nonalcoholic steatohepatitis, or NASH. We are planning to report data from this study in 2020.

Further, we have a small ongoing study of AKCEA-ANGPTL3-L_{Rx} in patients with rare hyperlipidemias.

IONIS-FXIRx and IONIS-FXI-LRx – IONIS-FXI$_{Rx}$ and IONIS-FXI-L_{Rx} are antisense medicines 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 medicine can be used broadly as an anti-thrombotic in many different therapeutic settings for which additional safe and well tolerated anti-thrombotic medicines are needed.

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. In this study, IONIS-FXI$_{Rx}$ demonstrated a favorable safety and tolerability profile. 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. In this study, IONIS-FXI$_{Rx}$ demonstrated a favorable safety and tolerability profile. There were no treatment-related major or clinically relevant non-major bleeding events.

We are currently evaluating IONIS-FXI$_{Rx}$ in a Phase 2b study in people with end-stage renal disease on hemodialysis to finalize dose selection. We are planning to report data from this study this year.

In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$. We plan to develop IONIS-FXI-L$_{Rx}$ through Phase 1. The Phase 1 study is in progress in healthy volunteers. It is a double-blind, randomized, placebo-controlled, dose-escalation study that will assess the safety and efficacy of IONIS-FXI-L$_{Rx}$.

AKCEA-APO(a)-LRx – See the medicine description under "Next Wave of Pivotal Medicines" section above.

AKCEA-APOCIII-LRx – AKCEA-APOCIII-L$_{Rx}$ is a LICA medicine we designed to inhibit the production of apoC-III, the same protein inhibited by WAYLIVRA, for the broad population of people who are at risk for cardiometabolic disease due to their elevated triglyceride levels. We and Akcea are developing 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 WAYLIVRA.

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

Novartis entered into a collaboration with us in January 2017 to advance AKCEA-APOCIII-L$_{Rx}$. In the first quarter of 2018, we initiated a Phase 2b dose-ranging study of AKCEA-APOCIII-L$_{Rx}$ in patients with hypertriglyceridemia and established CVD. We plan to report data from this study in 2020.

IONIS-DGAT2Rx – IONIS-DGAT2$_{Rx}$ is a Generation 2+ antisense medicine we designed to reduce the production of DGAT2, or diacylglycerol acyltransferase 2, to treat people with 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. Currently, it is estimated that two to three percent of the general population have NASH. 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 - 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 NAFLD, lowered blood lipid levels and reversed diet-induced insulin resistance. NASH is a more severe form of NAFLD.

IONIS-DGAT2$_{Rx}$ was evaluated in a Phase 2 randomized, placebo-controlled, dose-escalation study in patients with type 2 diabetes and NAFLD. In December 2018, we reported that IONIS-DGAT2$_{Rx}$ substantially reduced liver fat after only three months of treatment. 50 percent of IONIS-DGAT2$_{Rx}$ treated patients had relative liver fat reductions of greater than or equal to 30 percent. IONIS-DGAT2$_{Rx}$ demonstrated a favorable safety profile with no safety concerns related to the liver, kidney or platelets. Additionally, there were no increased levels of triglycerides or cholesterol. We plan to develop a liver LICA version of IONIS-DGAT2$_{Rx}$.

IONIS-AGT-LRx – IONIS-AGT-L$_{Rx}$ is a Generation 2+ LICA medicine we designed to reduce the production of angiotensinogen to decrease blood pressure in people with treatment resistant hypertension, or TRH. Despite the availability of generic antihypertensive agents, TRH is a major contributor to cardiovascular and renal disease.

Approximately 75 million adults in the U.S. have hypertension, half of whom have uncontrolled hypertension. About 12-15 percent of patients with uncontrolled hypertension have resistant hypertension, defined as failure to achieve a blood pressure goal of 140/90 (systolic/diastolic) despite the use of three or more antihypertensive medications. Current estimates approximate that there are up to three million people with TRH in the U.S. People with TRH have been found to have a three-fold higher chance of having fatal and non-fatal cardiovascular events relative to those with controlled hypertension.

We are evaluating IONIS-AGT-L$_{Rx}$ in a double-blinded, randomized, placebo-controlled, Phase 2 study in people with mild hypertension.

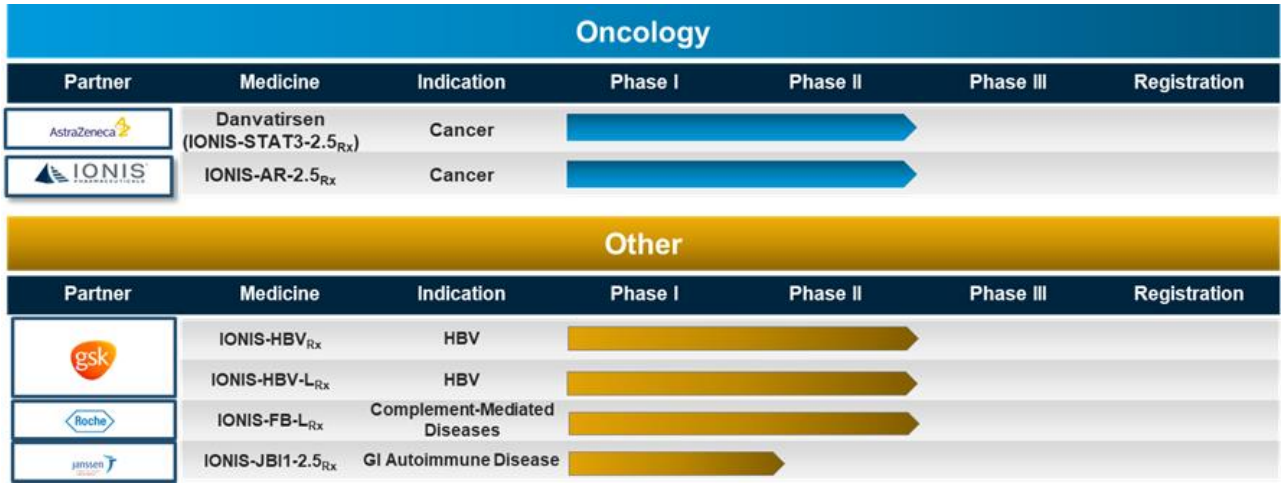
Oncology Franchise and Other Medicines in Development

Cancer is an area of significant unmet medical need. Cancer is an extremely complex disease that involves a large number of targets. Using our antisense technology, we can validate multiple potential cancer targets 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 can potentially provide a multi-faceted approach to treating cancer.

Our oncology franchise consists of anti-cancer antisense medicines that act upon biological targets associated with cancer progression, treatment resistance, and/or the tumor immune environment. 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 danvatirsen and IONIS-AZ7-2.5$_{Rx}$. 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 oncology 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 medicines to treat cancer together.

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

IONIS' Oncology/Other Clinical Pipeline



Danvatirsen (formerly IONIS-STAT3-2.5Rx) – Danvatirsen is a Generation 2.5 antisense medicine 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. Danvatirsen is a part of our collaboration with AstraZeneca to discover and develop anti-cancer medicines. We believe the significant potency we observed in our preclinical studies with danvatirsen broadens the therapeutic opportunities danvatirsen into many different types of cancer in which STAT3 is implicated.

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

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

IONIS-AR-2.5Rx – IONIS-AR-2.5$_{Rx}$, also known as AZD5312, is a Generation 2.5 antisense medicine we designed to treat people with prostate cancer by reducing the production of all known forms of androgen receptor, or AR, including variants of the AR gene. Prostate cancer is the second leading cause of cancer deaths in American men. Prostate cancer growth, proliferation and progression are all androgen-dependent and AR function is involved in disease progression at all stages of prostate cancer.

An open-label, dose-escalation, Phase 1/2 clinical study of IONIS-AR-2.5$_{Rx}$ was completed in people with advanced tumors for which the androgen receptor pathway is potentially a contributing factor. The study was primarily conducted in prostate cancer patients and it showed durable responses in a number of those patients. The medicine exhibited a favorable 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 medicine in China.

IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ – IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$ are antisense medicines 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 medicine 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 designed to reduce production of viral proteins associated with HBV infection.

IONIS-FB-L$_{Rx}$ – IONIS-FB-L$_{Rx}$ is a Generation 2+ LICA medicine 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 overactivity of this cascade has been associated with the development of several complement-mediated diseases, including dry age-related macular degeneration, or AMD.

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

In October 2018, we entered into a new collaboration with Roche to develop IONIS-FB-L$_{Rx}$ for the treatment of complement-mediated diseases. The first indication that we and Roche agreed to pursue is the treatment of patients with geographic atrophy, or GA, the advanced stage of dry AMD. We plan to start a Phase 2 study of IONIS-FB-L$_{Rx}$ in people with dry AMD this year.

IONIS-JBI1-2.5$_{Rx}$ – IONIS-JBI1-2.5$_{Rx}$ is a Generation 2.5 antisense medicine we designed to treat people for an undisclosed target of gastrointestinal autoimmune disease. In December 2014, we entered into a collaboration agreement with Janssen to discover and develop antisense drugs that can be locally administered, including oral delivery, to treat autoimmune disorders of the GI tract. In July 2016, Janssen licensed IONIS-JBI1-2.5$_{Rx}$ from us. Janssen is currently conducting a Phase 1 study of IONIS-JBI1-2.5$_{Rx}$.

Preclinical Medicines in Development

The efficiency and broad applicability of our technology enables us to develop medicines for a broad range of diseases. On average, it takes 12 to 18 months to complete the preclinical studies necessary to support clinical development. Over the last year we added eight new medicines to our preclinical pipeline.

IONIS' Preclinical Pipeline

Neuro

Medicines	Indication	Partner
IONIS-BIIB6$_{Rx}$	Neurodegenerative Disease	Biogen
IONIS-BIIB7$_{Rx}$	Neurodegenerative Disease	Biogen
IONIS-BIIB8$_{Rx}$	Neurodegenerative Disease	Biogen
IONIS-GFAP$_{Rx}$	Alexander's Disease	Ionis

Severe and Rare

Medicines	Indication	Partner
IONIS-RHO-2.5$_{Rx}$	Autosomal Dominant Retinitis Pigmentosa	ProQR

Cardiometabolic and Renal

Medicines	Indication	Partner
IONIS-AZ5-2.5$_{Rx}$	Kidney Disease	AstraZeneca
IONIS-AZ6-2.5-L$_{Rx}$	NASH	AstraZeneca

Oncology

Medicines	Indication	Partner
IONIS-IRF4-2.5$_{Rx}$	Cancer	Ionis
IONIS-EZH2-2.5$_{Rx}$	Cancer	Ionis
IONIS-AZ7-2.5$_{Rx}$	Cancer	AstraZeneca

Other

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

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

We formed Akcea Therapeutics in 2015 to focus on developing and commercializing medicines to treat people with serious and rare diseases. Akcea is commercializing TEGSEDI, a medicine we discovered and developed. Additionally, Akcea is advancing a mature pipeline of five of our novel medicines, including WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx}, and AKCEA-TTR-L_{Rx}, all with the potential to treat multiple diseases. We discovered all of these medicines, which are based on our proprietary antisense technology. Akcea is co-developing these five drugs with us.

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.

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

WAYLIVRA –See the medicine description under "WAYLIVRA – Potential Approval in Europe Following Positive CHMP Opinion" section above.

AKCEA-APO(a)-LRx – See the medicine description under "Potential Next Wave of Pivotal Medicines" section above.

AKCEA-TTR-LRx – See the medicine description under "Potential Next Wave of Pivotal Medicines" section above.

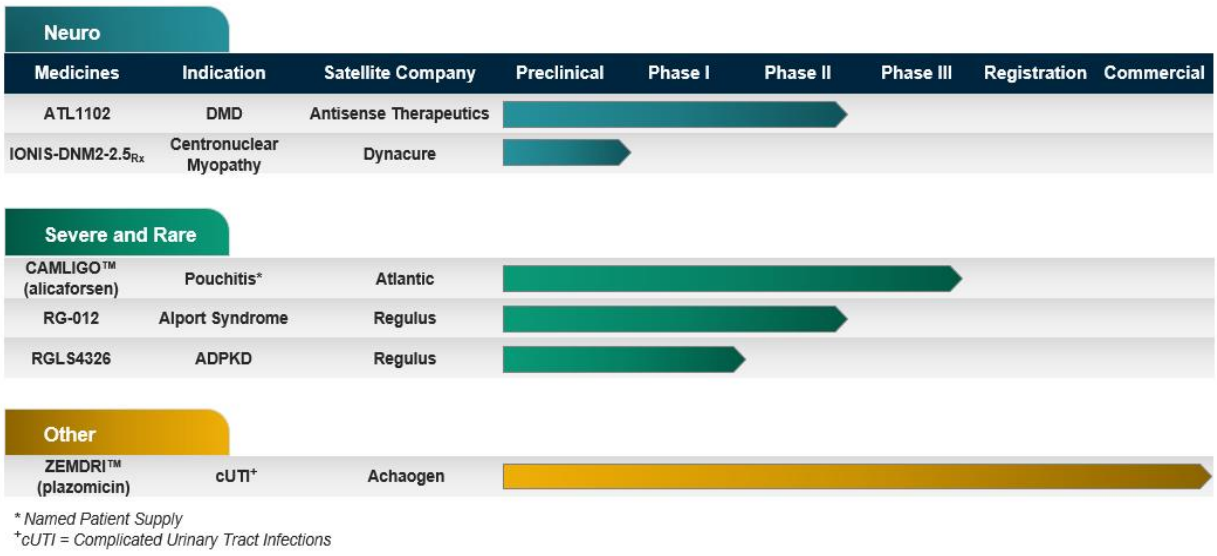
AKCEA-ANGPTL3-LRx – See the medicine description under "Cardiometabolic and Renal Disease Pipeline" section above.

AKCEA-APOCIII-LRx – See the medicine description under "Cardiometabolic and Renal Disease Pipeline" section above.

Satellite Company Medicines in Development

We have successfully developed novel medicines we designed to treat many different diseases. In therapeutic areas that are outside of our core areas of development, we have licensed our medicines to highly focused satellite companies that have the specific expertise and resources to continue developing the medicines. For our satellite company medicines, we refer to the medicine by the partner's name or compound number, such as ZEMDRI or ATL1102. We have listed these medicines below in our Satellite Company pipeline.

IONIS' Satellite Company Pipeline



** Named Patient Supply*
+cUTI = Complicated Urinary Tract Infections

Antisense Technology

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

These advantages include:

- Direct intervention in the disease process at the genetic level by targeting RNA: antisense technology represents a direct route from gene to drug. The explosion in genomic information and RNA biology has led to the discovery of many new disease-causing proteins and RNAs and has created new opportunities that are only accessible to antisense technology.
- Precise specificity: we design antisense medicines to target a single RNA, which minimizes or eliminates the possibility our medicines will bind to unintended targets which can cause unwanted side effects.
- Good drug properties: antisense medicines distribute well throughout the body without the need for special formulations or vehicles. They also have a relatively long half-life 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 medicines weekly, monthly or even less frequently depending on the medicine and target tissue.
- Ability to combine with other drugs: because antisense medicines do not interact with the enzymes that metabolize or break down other drugs, physicians can use our medicines 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.
- Utilize many different routes of administration including subcutaneous, intravenous, intrathecal, intravitreal, pulmonary and oral.
- Efficient discovery and early development: because of the efficiency of our antisense technology, our drug discovery and early development costs and success rates compare favorably to small molecule or antibody drug discovery and development.

We develop antisense medicines to potentially treat a wide range of diseases in a number of different therapeutic areas from severe and rare diseases to diseases that affect large patient populations. We focus our efforts on diseases in which there is a large unmet medical need with limited or no current treatments or in diseases for which we believe our medicines have a competitive advantage over existing therapies.

Technology Overview

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

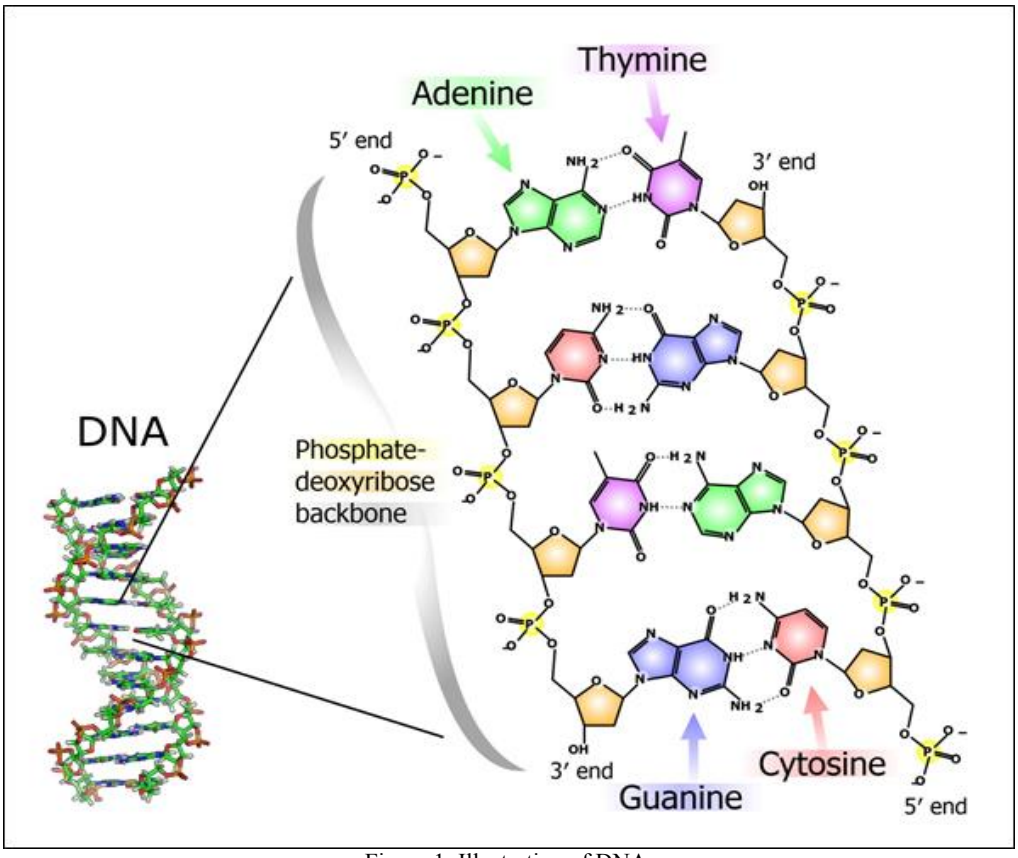
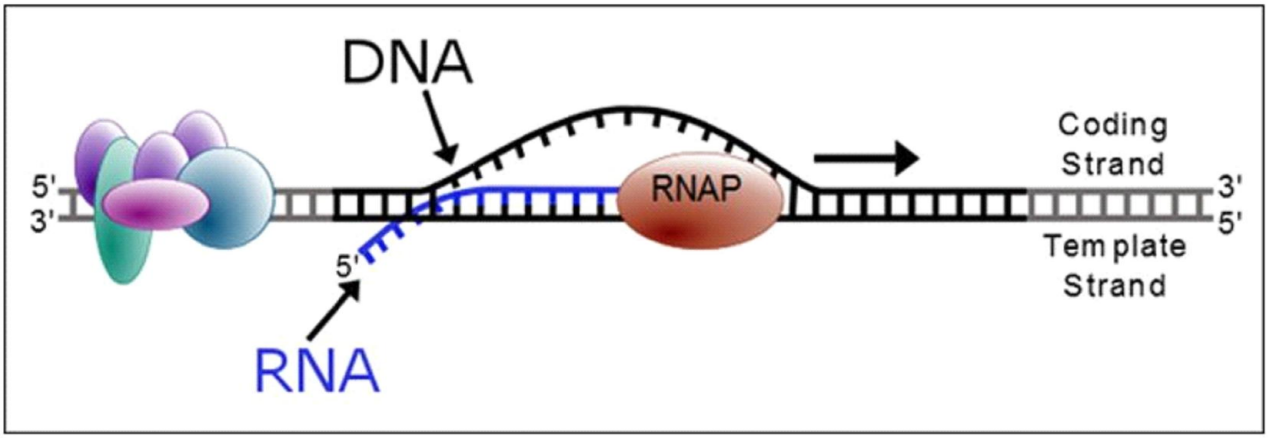


Figure 1: Illustration of DNA.

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

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

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



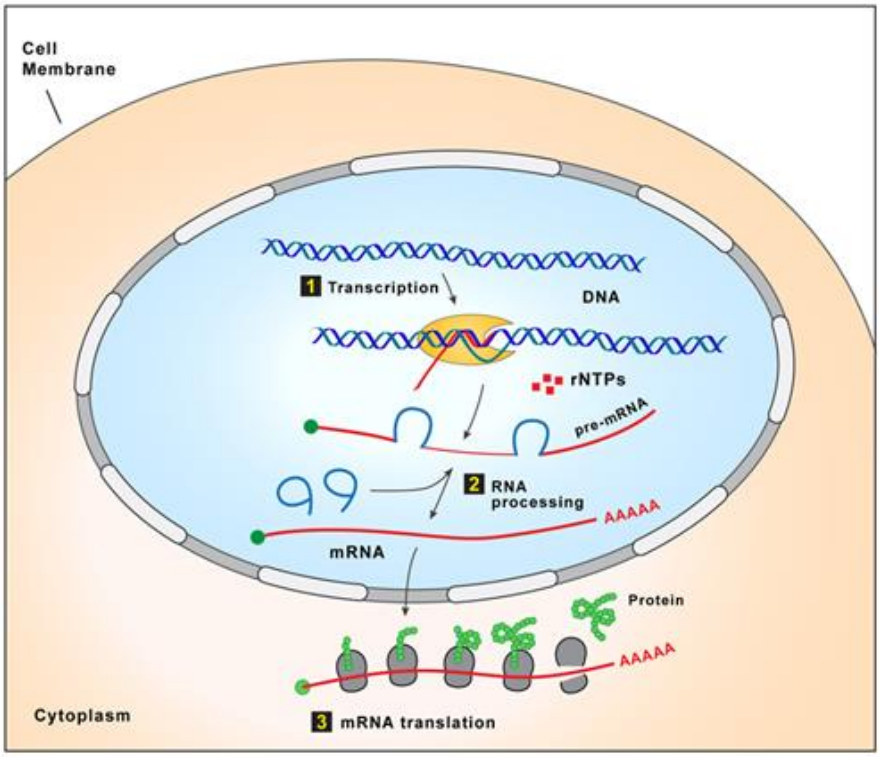


Figure 3: Translation of the protein-coding information contained in mRNA to protein.

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

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

Generation 2.5 chemistry is an advancement that we have demonstrated increases the potency of our medicines by up to 10-fold over our Generation 2+ medicines. This increase in potency enables our medicines to engage targets in a broader array of tissues. We have published data demonstrating that our Generation 2.5 medicines generally have enhanced potency over our Generation 2+ medicines and are broadly distributed throughout the body to multiple tissues including liver, kidney, lung, muscle, adipose, adrenal gland, peripheral nerves and tumor tissues. Our Generation 2.5 medicines constitute some of our recently added new medicines to our pipeline.

LICA is a chemical technology we developed that involves attaching a molecule called a ligand that binds with receptors on the surfaces of cells in a highly specific manner. Because these receptors are often found only on certain cell types, LICA allows us to increase effective delivery of our antisense medicines with higher specificity to certain cell types that express these receptors relative to non-conjugated antisense medicines. In November 2018, we published an integrated assessment of data from over 600 subjects, with more than 200 subjects on treatment for six months or longer, available from randomized placebo-controlled dose-ranging studies. The integrated assessment demonstrated with multiple Generation 2+ LICA medicines that our LICA technology for liver targets can increase potency by up to more than 30-fold over our non-LICA Generation 2+ medicines. In addition to the increase in potency, a favorable safety and tolerability profile was observed and was consistent across the entire LICA platform. There were no safety concerns related to platelets, liver or kidney function.

AKCEA-APO(a)-L_{Rx} further exemplifies these improvements. We designed this medicine 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). The Phase 2 AKCEA-APO(a)-L_{Rx} study was the first and only medicine to selectively and robustly reduce Lp(a) levels below threshold levels associated with CVD in nearly all patients. This study included more than 280 patients, with 98 percent of patients in the high dose group achieving levels below 50 mg/dL, the recognized risk threshold for CVD. Like the integrated assessment, the safety and tolerability profile from this study was favorable and there were no safety concerns related to platelets, liver or kidney function.

We have also combined our LICA technology with our Generation 2.5 chemistry medicines to further increase potency. Although we designed our first LICA medicines to inhibit targets in the liver, we are also developing LICA conjugation technology that we can use to target other tissues, such as the pancreas, and the initial results are promising.

Antisense Targets and Mechanisms

There are more than a dozen different antisense mechanisms that we can exploit with our antisense technology. The majority of the medicines in our pipeline bind to mRNAs and inhibit the production of disease-causing proteins. However, our antisense technology is broadly applicable to many different antisense mechanisms, including modulation of RNA splicing, RNA interference, or RNAi, and enhancing protein translation to increase protein production. In May 2018, we 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 developing 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 medicines bind to the target RNA via highly specific nucleotide pairing, or hybridization, and recruit a cellular enzyme called ribonuclease H1, or RNase H1, to degrade the target RNA. The antisense medicine itself remains intact during this process, so it can remain active against additional target RNA molecules and repeatedly trigger their degradation (Figure 4). Examples of our antisense medicines that use the RNase H1 mechanism to reduce disease protein production include, WAYLIVRA, TEGSEDI, IONIS-FXI_{Rx}, IONIS-FXI-L_{Rx}, AKCEA-APO(a)-L_{Rx}, IONIS-HTT_{Rx}, and others.

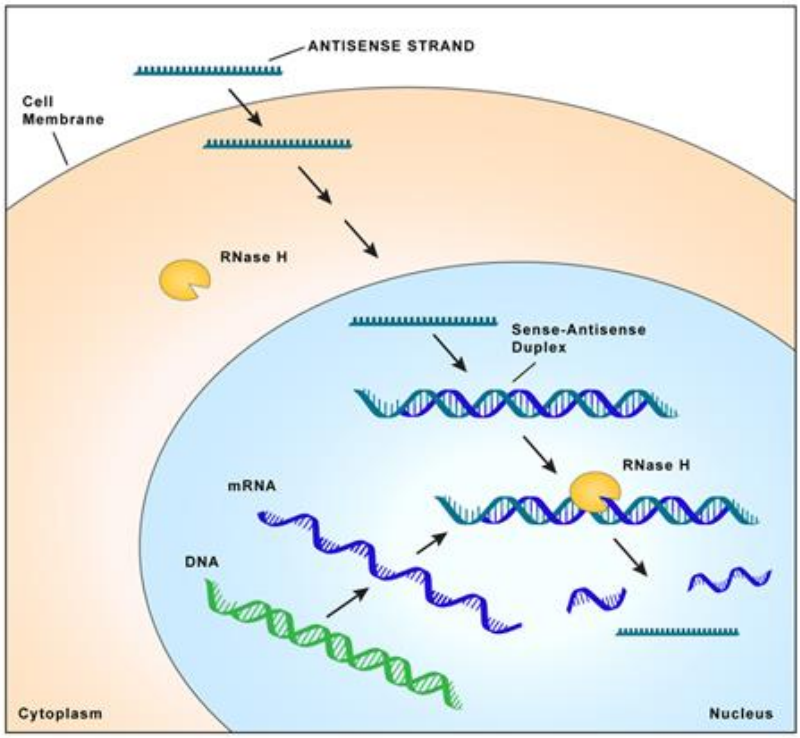


Figure 4: Antisense medicine using the RNase H mechanism of action.

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

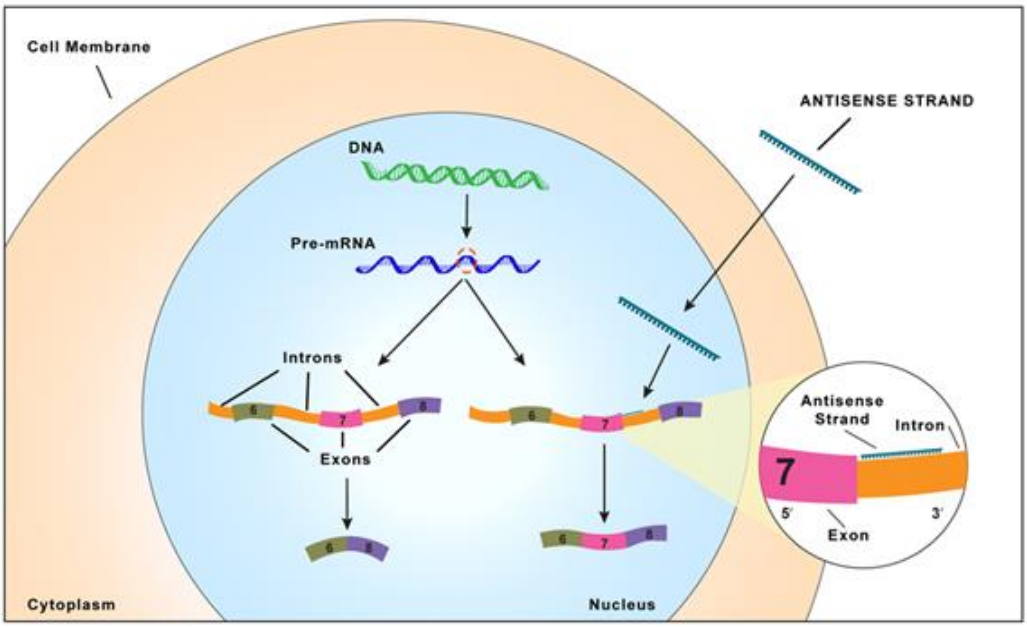


Figure 5: Antisense medicine altering splicing of the SMN2 mRNA.

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

Because the efficiency of our core technology platform can support multiple target-based antisense research programs without significantly increasing costs, we can develop antisense medicines to target a broad range of diseases, efficiently producing a large and broad proprietary portfolio of medicines. We are currently pursuing antisense drug discovery programs focused on various 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 medicines, advancing our technology, preparing to commercialize our medicines and selling our medicines. Our partners include the following companies, among others: AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis 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 medicines at what we believe is the optimal time to maximize the near-term, mid-term and long-term value of our medicines. We have distinct partnering strategies that we employ based on the specific program, therapeutic area and the expertise and resources our potential partners may bring to the collaboration.

- We have a strategic partnership with Biogen, which we expanded in 2018. Biogen provides expertise, tools and resources to complement our drug discovery efforts. Our broad strategic alliance with Biogen pairs Biogen's extensive resources and expertise in neurodegenerative diseases with our antisense technology. Together we are creating a franchise of novel medicines for neurodegenerative diseases that has the potential to expand both our pipeline and Biogen's pipeline with promising new medicines. Our development of and Biogen's commercialization of SPINRAZA, is just one example of the power of our strategic partnership.

- We have partnerships with companies that bring significant expertise and global resources to develop and potentially commercialize medicines for a particular therapeutic area. For example, in January 2017, we initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. In February 2019, Novartis licensed AKCEA-APO(a)-L_{Rx} and we earned a $150 million license fee. Novartis is responsible for conducting and funding all future development and commercialization activities for AKCEA-APO(a)-L_{Rx}, including a global pivotal cardiovascular outcomes study, for which planning and initiation activities are underway. We believe Novartis brings significant resources and expertise to the collaboration that should accelerate our ability to deliver these medicines to large patient populations who have high cardiovascular risk due to inadequately treated lipid disorders.

- 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 have a collaboration with Janssen that brings together our RNA-targeted technology platform and Janssen's expertise in autoimmune disorders and therapeutic formulation to discover and develop antisense medicines to treat autoimmune disorders in the GI tract. Thus far, Janssen has licensed and is advancing two medicines under our collaboration.

- We also work with a consortium of companies that can exploit our medicines and technologies outside our primary areas of focus. We refer to these companies as satellite companies.

Financial Benefits of Our Partnerships

Through our partnerships, we have earned both commercial revenue and a broad and sustaining base of R&D revenue in the form of license fees, upfront payments and milestone payments. Since 2007, we have received more than $4 billion in cash from upfront and licensing fees, equity purchase payments, milestone payments, research and development funding and royalties from our partnerships. We have the potential to earn more than $20 billion in future milestone payments, licensing fees and other payments from our current partnerships, not including potential royalties.

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with SMA. In December 2017, we entered into a collaboration with Biogen to identify new antisense medicines for the treatment of SMA. Additionally, we and Biogen are currently developing six other medicines to treat neurodegenerative diseases under our other collaborations, including IONIS-SOD1$_{Rx}$ for ALS, IONIS-MAPT$_{Rx}$ for Alzheimer's disease, IONIS-C9$_{Rx}$ for ALS, and IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ to treat undisclosed neurodegenerative diseases. In addition to these medicines, we and Biogen are evaluating numerous additional targets to develop medicines to treat neurological diseases. In April 2018, we entered into a new strategic collaboration for the treatment of neurological diseases with Biogen. From inception through February 2019, we have received over $2 billion from our Biogen collaborations, including $1 billion we received from Biogen in the second quarter of 2018 for our 2018 strategic neurology collaboration.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. Biogen reported in January 2019 that SPINRAZA was approved in over 40 countries around the world. In February 2019, SPINRAZA was approved in China. Biogen is responsible for global SPINRAZA commercial activities.

From inception through December 2018, we earned more than $785 million in total revenue under our SPINRAZA collaboration, including more than $350 million in revenue from SPINRAZA royalties and more than $435 million in R&D revenue. We are receiving tiered royalties ranging from 11 percent to 15 percent on any sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on net sales of SPINRAZA. Biogen is responsible for all further global development, regulatory and commercialization activities and costs for SPINRAZA.

New antisense medicines for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen 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. We will receive development and regulatory milestone payments from Biogen if new medicines advance towards marketing approval. In total over the term of our collaboration, we are eligible to receive up to $1.2 billion in license fees, milestone payments and other payments. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales.

Neurology Collaborations

2018 Strategic Neurology

In April 2018, we and Biogen entered into a new strategic collaboration to develop novel antisense medicines for a broad range of neurological diseases and entered into a Stock Purchase Agreement, or SPA. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for these diseases for 10 years. We are responsible for the identification of antisense drug candidates based on selected targets. Biogen is responsible for conducting IND-enabling toxicology studies for the selected target. Biogen will have the option to license the selected target after it completes the IND-enabling toxicology study. If Biogen exercises its option for a medicine, it will assume all further global development, regulatory and commercialization responsibilities and costs for that medicine. In the second quarter of 2018, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at an approximately 25 percent cash premium and $375 million in an upfront payment. We are eligible to receive up to $270 million in milestone payments for each medicine that achieves marketing approval. We have generated over $1 billion in payments through February 2019, including $15 million we received in the fourth quarter of 2018 for advancing two targets under this collaboration. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales.

2013 Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license medicines resulting from this collaboration. We will usually be responsible for drug discovery and early development of antisense medicines and Biogen will have the option to license antisense medicines after Phase 2 proof of concept. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option for a medicine, it will assume all further global development, regulatory and commercialization responsibilities and costs for that medicine. We are currently advancing five medicines, IONIS-$SOD1_{Rx}$, IONIS-$C9_{Rx}$, IONIS-$BIIB6_{Rx}$, IONIS-$BIIB7_{Rx}$ and IONIS-$BIIB8_{Rx}$ under this collaboration. In December 2018, Biogen exercised its option to license IONIS-$SOD1_{Rx}$, and as a result Biogen is now responsible for all further global development, regulatory and commercialization activities and costs for IONIS-$SOD1_{Rx}$.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all medicines developed 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 per program. We have generated over $215 million through February 2019, including $40 million we earned in the fourth quarter of 2018 when Biogen advanced and licensed IONIS-$SOD1_{Rx}$. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any antisense medicines developed under this collaboration.

Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize up to three novel antisense medicines to treat neurodegenerative diseases. We are responsible for the development of each of the medicines through the completion of the initial Phase 2 clinical study for such medicine. Biogen has the option to license a medicine from each of the programs through the completion of the first Phase 2 study for each program. We are currently advancing IONIS-$MAPT_{Rx}$ for Alzheimer's disease under this collaboration. If Biogen exercises its option for a medicine, it will assume all further global development, regulatory and commercialization responsibilities and costs for that medicine. Under the terms of the agreement, we received an upfront payment of $30 million. Over the term of the collaboration, we are eligible to receive up to $210 million in a license fee and milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. We have generated over $55 million through February 2019. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales of any medicines resulting from each program under the agreement.

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

AstraZeneca

Cardiac, Renal and Metabolic Diseases Collaboration

In July 2015, we and AstraZeneca formed a collaboration to discover and develop antisense therapies for treating cardiac, renal and metabolic diseases. Under our collaboration, AstraZeneca has licensed three medicines from us: IONIS-AZ4-2.5-L_{Rx}, a medicine we designed to treat cardiovascular disease and our first medicine that combines our Generation 2.5 and LICA technology, IONIS-AZ5-2.5_{Rx}, a medicine we designed to treat a genetically associated form of kidney disease and IONIS-AZ6-2.5-L_{Rx}, a medicine we designed to inhibit an undisclosed target to treat patients with NASH. AstraZeneca is responsible for all further global development, regulatory and commercialization activities and costs for each of the medicines it has licensed and any other future medicines AstraZeneca licenses.

Under the terms of the agreement, we received a $65 million upfront payment. We are eligible to receive license fees and milestone payments of up to more than $4 billion as medicines under this collaboration advance. We have generated over $165 million in payments through February 2019, including a $10 million milestone payment we earned in the third quarter of 2018 when AstraZeneca initiated a Phase 1 trial for IONIS-AZ4-2.5-L_{Rx}. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement.

Oncology Collaboration

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

Under the terms of this agreement, we received $31 million in upfront payments. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. If AstraZeneca successfully develops danvatirsen and another medicine under the research program, we could receive license fees and milestone payments of up to more than $450 million. We have generated over $125 million in payments through February 2019, including nearly $30 million in milestone payments we achieved when AstraZeneca advanced danvatirsen and IONIS-AZ7-2.5$_{Rx}$, in the fourth quarter of 2018. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any medicines resulting from these programs.

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.

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 are developing 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 medicines. We are eligible to receive additional milestone payments as each medicine advances toward the market. In total over the term of this collaboration, we are eligible to receive up to $385 million in license fees, milestone payments and other payments. We have generated over $175 million through February 2019. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of both medicines combined.

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 medicines against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. Under the terms of the agreement, we received upfront payments of $35 million. GSK is advancing two medicines targeting HBV under our collaboration: IONIS-HBV$_{Rx}$ and IONIS-HBV-L$_{Rx}$. GSK is currently conducting Phase 2 studies for both of these medicines, which we designed to reduce the production of viral proteins associated with HBV infection. GSK has the exclusive option to license the medicines resulting from this alliance at Phase 2 proof-of-concept for a license fee.

Under our agreement, if GSK successfully develops these medicines and achieves pre-agreed sales targets, we could receive license fees and milestone payments of $262 million. We have generated over $162 million in payments through February 2019. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that GSK successfully commercializes under this alliance.

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 medicines that can be locally administered, including oral delivery, to treat autoimmune disorders of the GI tract. Janssen has the option to license medicines from us through the designation of development candidates for up to three programs. Under our collaboration, Janssen licensed IONIS-JBI1-2.5$_{Rx}$ in July 2016 and IONIS-JBI2-2.5$_{Rx}$ in November 2017. Janssen is currently conducting a Phase 1 study of IONIS-JBI1-2.5$_{Rx}$ and IONIS-JBI2-2.5$_{Rx}$ is in preclinical development. Prior to option exercise we are responsible for the discovery activities to identify development candidates. If Janssen exercises an option for any 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. We are eligible to receive up to more than $800 million in milestone payments and license fees for these programs. We have generated over $75 million through February 2019. In addition, we are eligible to receive tiered royalties up to the near teens on net sales from any medicines resulting from this collaboration.

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.

Roche

Huntington's Disease

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for HD based on our antisense technology. Under the agreement, we discovered and developed IONIS-HTT_{Rx}, an antisense medicine targeting HTT protein, through completion of our Phase 1/2 clinical study in people with early stage HD. In December 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license 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 as IONIS-HTT_{Rx} advances. We have generated over $145 million through February 2019, including $35 million in milestone payments we generated in the first quarter of 2019 when Roche dosed the first patient in a Phase 3 study for IONIS-HTT_{Rx}. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional medicine successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on net sales from any product resulting from this alliance.

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

In October 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases. The first indication we plan to pursue is the treatment of patients with GA, the advanced stage of dry AMD. We are responsible for conducting a Phase 2 study in patients with dry AMD. In addition, we are exploring the medicine in a severe and rare renal indication. Roche has the option to license IONIS-FB-L_{Rx} at the completion of these studies. Upon licensing, Roche will be responsible for all further global development, regulatory and commercialization activities and costs. Under the terms of this agreement, we received a $75 million upfront payment in October 2018. We are eligible to receive up to $684 million in milestone payments and license fees. In addition, we are also eligible to receive tiered royalties from the high teens to twenty percent on net sales.

For additional details about our collaboration agreements 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.

Akcea Collaborations

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

Novartis

In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the collaboration agreement, Novartis has an exclusive option to further 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 initial quantities of API for each medicine. If Novartis exercises an option for either of these medicines, Novartis will be responsible for all further global development, regulatory and co-commercialization activities and costs for such medicine.

Akcea received a $75 million upfront payment in the first quarter of 2017. In February 2019, Novartis licensed AKCEA-APO(a)-L_{Rx} and we earned a $150 million license fee. Novartis is responsible for conducting and funding all future development, regulatory and commercialization activities for AKCEA-APO(a)-L_{Rx}, including a global pivotal cardiovascular outcomes study, for which planning and initiation activities are underway. If Novartis exercises its option for AKCEA-APOCIII-L_{Rx}, Novartis will pay Akcea a license fee equal to $150 million. In addition, Akcea is eligible to receive up to $675 million and $530 million in milestone payments related to AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, respectively. 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. In connection with Novartis' license of AKCEA-APO(a)-L_{Rx}, Akcea and Novartis established a more definitive framework under which the companies would negotiate the co-commercialization of AKCEA-APO(a)-L_{Rx} in selected markets. Included in this framework is an option by which Novartis could solely commercialize AKCEA-APO(a)-L_{Rx} in exchange for Novartis paying Akcea increased commercial milestone payments based on sales of AKCEA-APO(a)-L_{Rx}. Akcea may co-commercialize IONIS-APOCIII-L_{Rx} if licensed and commercialized by Novartis in selected markets through its specialized sales force under terms and conditions to be negotiated with Novartis in the future.

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

For additional details about our 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.

PTC Therapeutics

In August 2018, Akcea entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America. Under the license agreement, Akcea is eligible to receive up to $26 million in payments, including $12 million which it received in the third quarter of 2018, $6 million upon the earlier of FDA or EMA approval of WAYLIVRA and up to $8 million for regulatory milestones. Akcea is eligible to receive royalties from PTC in the mid-20 percent range on net sales in Latin America for each medicine. PTC's obligation to pay Akcea royalties begins on the earlier of 12 months after the first commercial sale of a product in Brazil or the date that PTC recognizes revenue of at least $10 million in Latin America. Consistent with the agreements between Ionis and Akcea, the companies will share all payments, including royalties.

Satellite Company Partnerships

We have a number of satellite company collaborations that expand the reach and potential of our RNA-targeting medicines into disease areas that are outside of our core focus.

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

In addition to Alnylam, our satellite company collaborations include collaborations with the following companies:

Satellite Company	Focus
Achaogen, Inc.	Aminoglycosides
Antisense Therapeutics Limited	Inflammation, Acromegaly
Atlantic Pharmaceuticals Limited	Inflammation
Dynacure, SAS	Muscle Disorders
ProQR Therapeutics N.V.	Ophthalmology
Regulus Therapeutics Inc.	microRNA-targeting therapeutics
Suzhou Ribo Life Science Co., Ltd.	ssRNAi

Under our satellite collaborations we are eligible to earn milestone payments, license fees and royalties. In addition, in certain cases we own equity in the company.

External Project Funding

We are pursuing discovery and development projects that provide us with new therapeutic applications for antisense medicines. 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. Our External Project Funding partners include the following:

- *CHDI Foundation*- Through our development collaboration, CHDI provided financial and scientific support to our Huntington's disease drug discovery program. We have reimbursed CHDI for its support of our Huntington's disease program out of the payments we received from Roche.
- *Cystic Fibrosis Foundation*- We received upfront funding from the Cystic Fibrosis Foundation to discover and advance a medicine for the treatment of cystic fibrosis. In exchange for this funding, we are obligated to pay the Cystic Fibrosis Foundation up to $18 million upon achieving specific regulatory and sales events if we advance a medicine under our collaboration.
- *The Ludwig Institute; Center for Neurological Studies*- We have a collaboration with the Ludwig Institute, the Center for Neurological Studies and researchers to discover and develop antisense medicines for ALS and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and the Center for Neurological Studies modest milestone payments and royalties on any antisense medicines resulting from the collaboration.

Manufacturing

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

Our 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 and foreign equivalents to ensure that it is operating in compliance with current Good Manufacturing Practices, or cGMP, requirements.

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

We believe we have sufficient manufacturing capacity at our own facility or at contract manufacturing organizations, or CMOs, to meet our current internal research, development and potential commercial needs, as well as our current and future obligations under existing agreements with our partners for research, development and commercial needs. We believe our current network of CMO partners are capable of providing sufficient quantities to meet anticipated commercial demands. Additionally, we continue to evaluate relationships with additional suppliers to increase overall capacity and diversify our supply chain. While we believe that there are alternate sources of supply that can satisfy our commercial requirements, 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.

Specifically, we have the following in place for our approved medicines, SPINRAZA and TEGSEDI, our medicine currently under regulatory review, WAYLIVRA and our medicine in Phase 3 development, IONIS-HTT_{Rx}:

SPINRAZA

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

TEGSEDI

For TEGSEDI's commercial drug supply, we are using CMOs to produce custom raw materials, API and finished goods. Our CMO partners have extensive technical expertise and cGMP experience.

WAYLIVRA

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

IONIS-HTT_{RX}

Pursuant to our collaboration with Roche, Roche is responsible for IONIS-HTT_{Rx} drug supply.

LICA Medicines

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

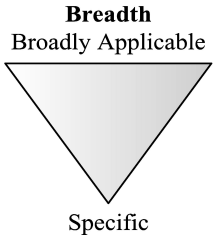
Patents and Proprietary Rights

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

We own or control patents that provide exclusivity for products in our pipeline and patents that provide exclusivity for our core technology in the field of antisense more generally. Our core technology patents include claims to chemically modified nucleosides and oligonucleotides as well as antisense 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 medicines. For example, we file and seek to obtain claims covering each drug's nucleic acid sequence and precise drug design. In sum, we maintain our competitive advantage in the field of antisense technology by protecting our core platform technology and by creating multiple layers of patent protection for each of our specific medicines in development.

Type of Patent Claim
(Broadly Applicable to Specific)

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



Chemically Modified Nucleosides and Oligonucleotides

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

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

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

We also have patents that claim oligonucleotides comprising antisense drug design motifs, or patterns of nucleoside modifications at specified positions in the oligonucleotide. Patent claims covering our antisense drug design motifs are independent of nucleic acid sequence, so they cover oligonucleotides having the recited motif, regardless of cellular target or clinical indication. The claimed motifs generally confer properties that optimize oligonucleotides for a particular antisense mechanism of action, such as ribonuclease H, 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 medicines, including TEGSEDI, WAYLIVRA and IONIS-HTT$_{Rx}$, but excluding SPINRAZA, contain this gapmer antisense drug design motif. We own a U.S. patent that covers all of our second generation MOE gapmer antisense medicines until March of 2023.

In addition, we have pursued patent claims to antisense drug design motifs incorporating bicyclic nucleoside analogs, which include both locked nucleic acids, or "LNA" and cEt. In Europe, we have been granted claims drawn to certain short gapmer oligonucleotides with bicyclic nucleosides, which include locked nucleic acids, in the wings for the treatment of cardiovascular or metabolic disorders. We have also successfully obtained issued patent claims covering our Generation 2.5 gapmer antisense drug design motifs that incorporate our cEt modified nucleosides. 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 a 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 medicines to specific tissues and cells to improve a drug's properties. We designed our N-acetyl-galactosamine, or GalNAc, LICA medicines to provide an increase in potency for targets in the liver. We have successfully obtained issued patent claims covering our LICA technology conjugated to any modified oligonucleotide, including gapmers, double-stranded siRNA compounds, and fully modified oligonucleotides. The following patents are some examples of our issued patents in this category:

Jurisdiction	Patent/ 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 product's specifically, in addition to the broader core antisense patents described above.

SPINRAZA and Survival Motor Neuron

SPINRAZA is protected from generic competition in the U.S. 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. 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	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

TEGSEDI and Transthyretin

We obtained issued claims covering TEGSEDI in the U.S. The issued U.S. claims protect TEGSEDI from generic competition in the U.S. until at least 2031. We are also pursuing additional patent applications designed to protect TEGSEDI in foreign jurisdictions. The table below lists the current issued patents protecting TEGSEDI 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 TEGSEDI
United States	8,697,860	DIAGNOSIS AND TREATMENT OF DISEASE	2031	Composition of TEGSEDI
United States	9,061,044	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Sodium salt composition of TEGSEDI
United States	9,399,774	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Methods of treating transthyretin amyloidosis by administering TEGSEDI
Japan	JP5896175	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Composition of TEGSEDI
Europe	EP2563920	MODULATION OF TRANSTHYRETIN EXPRESSION	2031	Composition of TEGSEDI

WAYLIVRA and Apolipoprotein C-III

We have obtained patent claims in the U.S. drawn to the use of antisense compounds complementary to a broad active region of human Apo C-III, including the site targeted by WAYLIVRA. 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 WAYLIVRA in the U.S., Australia, Canada, Hong Kong and Europe. The issued U.S. claims protect WAYLIVRA from generic competition in the U.S. until at least 2023. In addition, if WAYLIVRA is approved by the FDA, we will seek patent term extension to recapture a portion of the term lost during FDA regulatory review, extending the term of this patent beyond 2023. We are pursuing additional patent applications designed to protect WAYLIVRA 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 WAYLIVRA
United States	7,598,227	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Methods of treating hyperlipidemia, lowering cholesterol levels or lowering triglyceride levels with WAYLIVRA
United States	7,750,141	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2023	Antisense sequence and chemistry of WAYLIVRA
Europe	EP1622597	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2024	Antisense sequence and chemistry of WAYLIVRA
Europe	EP2441449	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2024	Antisense compound specifically hybridizable within the nucleotide region of apoCIII targeted by WAYLIVRA
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 WAYLIVRA 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

IONIS-HTT$_{Rx}$ and Huntingtin

We obtained issued claims covering IONIS-HTT$_{Rx}$ in the U.S.. The issued U.S. claims protect IONIS-HTT$_{Rx}$ from generic competition in the U.S. until at least 2030. We are also pursuing additional patent applications designed to protect IONIS-HTT$_{Rx}$ in foreign jurisdictions. The table below lists the current issued patents protecting IONIS-HTT$_{Rx}$ in key jurisdictions:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	9,273,315	MODULATION OF HUNTINGTIN EXPRESSION	2030	Composition of IONIS-HTT$_{Rx}$
United States	8,906,873	MODULATION OF HUNTINGTIN EXPRESSION	2030	Methods of treating Huntington's disease by administering IONIS-HTT$_{Rx}$
Europe	EP2475675	MODULATION OF HUNTINGTIN EXPRESSION	2030	Composition of IONIS-HTT$_{Rx}$
Japan	JP5809146	MODULATION OF HUNTINGTIN EXPRESSION	2030	Composition of IONIS-HTT$_{Rx}$
United States	7,951,934	COMPOSITIONS AND THEIR USES DIRECTED TO HUNTINGTIN	2027	Antisense sequence of IONIS-HTT$_{Rx}$
United States	8,952,145	COMPOSITIONS AND THEIR USES DIRECTED TO HUNTINGTIN	2027	Antisense compound specifically hybridizable within the nucleotide region of HTT targeted by IONIS-HTT$_{Rx}$
Japan	5425474	COMPOSITIONS AND THEIR USES DIRECTED TO HUNTINGTIN	2027	Antisense sequence of IONIS-HTT$_{Rx}$
European	EP2161038	COMPOSITIONS AND THEIR USES DIRECTED TO HUNTINGTIN	2027	Antisense sequence of IONIS-HTT$_{Rx}$

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

Manufacturing Patents

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

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

Government Regulation

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

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

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

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

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

For any approved medicine, domestic and foreign sales of the medicine depend, in part, on the availability and amount of reimbursement by third party payors, including governments and private health plans. Private health plans may seek to manage cost and use of our medicines by implementing coverage and reimbursement limitations. Governments may also regulate or influence coverage, reimbursement and/or pricing of our medicines to control cost or affect use. Within the EU a variety of payors pay for medicines, with governments being the primary source of payment. Negotiating pricing with governmental authorities can delay commercialization. Such pricing and reimbursement factors could impact our ability, including Akcea, and that of our commercial partners to successfully commercialize approved medicines.

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

Other healthcare laws that may affect our ability to operate include the 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 foreign and state laws governing the privacy and security of health information, such as the General Data Protection Regulation, or GDPR, in the EU, and the California Consumer Privacy Act, or CCPA, in California, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect; and the Physician Payments Sunshine Act, which requires manufacturers of medicines, devices, biologics, and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members.

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

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

Competition

Our Business in General

Some of our medicines may compete with existing therapies for market share. 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 medicines are differentiated from traditional small molecule medicines by their chemistry, how they move in the body, how they act in the body, delivery technology, and formulations.

Our approved products and our products under development address numerous markets. The diseases our medicines target for which we have or may receive marketing authorization will determine our competition. For some of our products, an important factor may be the timing of market introduction of competitive products. Accordingly, the relative speed with which we can develop products, complete the clinical trials and marketing authorization processes and supply commercial quantities of the products to the market are important competitive factors. We expect to compete 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.

Below we have included what we believe to be the competitive landscape for the following key programs:

- Marketed Medicines: SPINRAZA and TEGSEDI
- Medicine under regulatory review: WAYLIVRA
- Medicine currently in pivotal trials: IONIS-HTT$_{Rx}$

Marketed Medicines

SPINRAZA

We believe that the following medicines could compete with SPINRAZA:

Medicine	Company	Medicine Description	Phase	Admin/Dosing	Efficacy(1)	Safety(1)
Zolgensma (AVXS-101)	Novartis	Gene therapy that corrects the SMN1 gene using the AAV9 Vector	Under FDA Review	Infusion	Demonstrated an increase in survival and improvement in achievement of developmental milestones vs the natural history of SMA Type 1. Study included a small number of patients.	Generally well tolerated to date and the most commonly observed side effect was elevated liver enzymes. Study included a small number of patients.
Risdiplam (RG7916)	PTC Therapeutics/ Roche/ SMA Foundation	A small molecule drug that modulates splicing of the SMN2 gene	2	Oral	Preliminary findings from Part 1 of the FIREFISH study show that infants with Type 1 SMA are meeting developmental milestones including sitting without support. Preliminary findings from Part 1 of the SUNFISH study show improvements in motor function in people with Type 2/3 SMA. Studies included a small number of patients.	Safe and well tolerated at all doses and had no drug-related or safety-related study withdrawals. Studies included a small number of patients.
Reldesemtiv	Cytokinetics/ Astellas	A selective, fast skeletal muscle troponin activator	2	Oral	The Phase 2 study demonstrated dose-dependent increases in six minute walk distance in ambulatory patients as measured at both post-baseline time points, week four and week eight	Adverse events were similar between groups receiving reldesemtiv and placebo. The most commonly observed adverse effects were headache, constipation and nausea
Firdapse	Catalyst/Jazz/ BioMarin	A potassium channel blocker that increases the release of acetylcholine	2	Oral	None reported	None reported

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

We believe that Zolgensma, if approved, may be the first medicine to compete with SPINRAZA. The FDA accepted Novartis' biologics licensing application, or BLA, for Zolgensma, in December 2018 and regulatory action is anticipated in May 2019. The filing is supported by data from the START trial, which demonstrated an increase in survival and improvement in achievement of developmental milestones compared to the natural history of SMA Type 1. The START trial included 15 patients.

TEGSEDI

We believe that the following medicines could compete with TEGSEDI:

Medicine	Company	Medicine Description	Phase	Admin/Dosing	Efficacy(1)	Safety(1)
Onpattro	Alnylam	An RNAi drug formulated with lipid nanoparticles to inhibit TTR mRNA	Approved	Infusion every 3 weeks with pre-treatment with steroids	84.3% mean reduction in TTR at 18 months	Most common AEs more frequently observed in Onpattro 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	Commercially available in the EU for stage 1 hATTR amyloidosis with polyneuropathy. Under review in the U.S. for ATTR with cariodmyopathy with a PDUFA date in July 2019	Daily oral capsule	In 45% of patients 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
AG10	Eidos	Small molecule that binds and stabilizes TTR in the blood	2	Oral	Demonstrated a statistically significant increase in serum TTR concentrations	Drug well tolerated with no safety signals
CRX-1008	Corino Therapeutics	Small molecule repurposed generic drug	2	Daily oral dose	Shows binding and stabilization of TTR in humans	No drug related adverse events reported
Vutrisiran	Alnylam	An RNAi drug conjugated with GalNAC to inhibit TTR mRNA in liver cells	3	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.

TEGSEDI is a once weekly, self-administered subcutaneous medicine. TEGSEDI was approved in 2018 in the U.S., EU and Canada for the treatment of polyneuropathy caused by hATTR in adult patients. Results from our Phase 3 NEURO-TTR study demonstrated that patients treated with TEGSEDI experienced significant benefit compared to patients treated with placebo across both co-primary endpoints: the Norfolk QoL-DN and mNIS+7 a measure of neuropathic disease progression. The product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis and requires periodic blood and urine monitoring. TEGSEDI has a Risk Evaluation and Mitigation Strategy, or REMS, program. Our main competition in the U.S. market for TEGSEDI is ONPATTRO (patisiran), marketed by Alnylam Pharmaceuticals, Inc. Although ONPATTRO requires intravenous administration by a healthcare provider in a clinical setting every three weeks and pre-treatment with steroids, it does not have a boxed warning or REMS.

Medicine Under Regulatory Review

WAYLIVRA

We believe that the following medicines could compete with WAYLIVRA:

Medicine	Company	Medicine 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 150 mg and 300 mg 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. Metreleptin is currently approved for use in the U.S. and EU in generalized lipodystrophy, or GL patients. 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. Gemphire announced top-line results in June 2018 that Gemcabene met its Phase 2b primary endpoint and demonstrated statistically significant lowering of triglycerides in severe hypertriglyceridemia. The initiation of a Phase 3 study will not take place until the partial clinical hold, which was issued by the FDA in 2004, is lifted.

To date, WAYLIVRA has shown the highest percent of triglyceride reductions compared to existing treatments, such as fibrates, regardless of starting triglyceride levels prior to dosing with WAYLIVRA. Based on our broad Phase 2 data for the treatment of different patients including people with FCS, we believe that WAYLIVRA will work equally well as a single agent or in combination with other triglyceride-lowering medicines 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 WAYLIVRA.

Medicine Currently in Pivotal Trials

IONIS-HTT$_{Rx}$

We believe that the following medicines could compete with IONIS-HTT$_{Rx}$:

Medicine	Company	Medicine Description	Phase	Admin/Dosing	Efficacy(1)	Safety(1)
Laquinimod	Active Biotech	A small molecule that activates selective aryl hydrocarbon receptor	2	Daily oral dose	Did not meet its primary endpoint of slowing disease development, but secondary endpoint of reduction of brain atrophy was met	No drug related adverse events reported
OMS824	Omeros	A small molecule that targets PDE 10	2	Daily oral dose	None reported	None reported
Selistat	AOP Orphan	An orally active, selective SIRT1 inhibitor	2	Daily oral dose	None reported	Safe and tolerable in Phase 1 and Phase 2 study
VX15	Vaccinex	A monoclonal antibody that blocks the activity of SEMA4D	2	Monthly intravenous infusions	Favored in all brain regions examined, with median increase in FDG uptake from baseline of 8.6% vs placebo control achieving significance in the majority of frontal and parietal brain regions analyzed	To date, evaluated patients showed no safety signals
WVE-120101/ WVE-120102	Wave Life Sciences	Antisense drugs targeting mHTT SNP-1 and SNP-2	1b/2a	Intrathecal administration	None reported	None reported

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

We believe that Wave Life Sciences' WVE-120101 and WVE-120102, being developed for Huntington's Disease, could compete directly against IONIS-HTT_{Rx}. These medicines are antisense medicines administered intrathecally, targeting mHTT SNP-1 and SNP-2, respectively. Wave Life Sciences is currently conducting two simultaneous Phase 1b/2a clinical trials, enrolling adults with early manifest Huntington's disease who carry a single nucleotide polymorphism, or SNP, at the SNP1 (study name: PRECISION HD1) and SNP2 (study name: PRECISION HD2) location, with their data readouts expected in the first half of 2019.

Employees

As of February 20, 2019, we employed 737 people, including 248 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, 2019:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D.	73	Chairman, Chief Executive Officer and President
Brett P. Monia, Ph.D.	57	Chief Operating Officer
C. Frank Bennett, Ph.D.	62	Senior Vice President, Antisense Research
Damien McDevitt, Ph.D.	52	Chief Business Officer
Richard S. Geary, Ph.D.	61	Senior Vice President, Development
Elizabeth L. Hougen	57	Senior Vice President, Finance and Chief Financial Officer
Patrick R. O'Neil, Esq.	45	Senior Vice President, Legal, General Counsel, Chief Compliance Officer and Corporate Secretary

Management Transitions

In January 2020, Dr. Crooke, our founder and Chief Executive Officer, plans to transition from Chief Executive Officer to Executive Chairman of our Board of Directors. As Executive Chairman, Dr. Crooke will continue to be responsible for the activities of the board and will remain active in the company, providing strategic advice and continuing to participate in the scientific activities. Our board has selected Dr. Monia, who has been our Chief Operating Officer for the last year and a member of our team since our founding nearly 30 years ago, to serve as our Chief Executive Officer starting in January 2020.

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, Translational Medicine

Dr. Monia was promoted to Chief Operating Officer in January 2018 and to Senior Vice President 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 and the Hereditary Disease Foundation.

DAMIEN McDEVITT, Ph.D.

Chief Business Officer

Dr. McDevitt joined Ionis in June 2018 as our Chief Business Officer. In October 2018, he was appointed to the board of directors of our majority-owned affiliate, Akcea Therapeutics, Inc. Previously, Dr. McDevitt was Senior Vice President, Corporate Development at ACADIA Pharmaceuticals. Prior to ACADIA, he was at GSK for more than two decades. He served in various roles with increasing responsibility including vice president, head of business development for R&D Extended Therapy areas, head of Worldwide Business Development Asia and head of GSK's R&D West Coast Innovation Center.

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 medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, we are not likely to generate revenues or become consistently profitable.

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

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

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

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

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

For example, the product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis, requires periodic blood and urine monitoring, and TEGSEDI has a Risk Evaluation and Mitigation Strategy, or REMS, program. Our main competition in the U.S. market for TEGSEDI is ONPATTRO (patisiran), marketed by Alnylam Pharmaceuticals, Inc. Although ONPATTRO requires intravenous administration and pre-treatment with steroids, it does not have a boxed warning or REMS. Additionally, in the clinical studies with WAYLIVRA, declines in platelet counts were observed in many patients and some patients discontinued the studies because of platelet declines. Therefore, we expect the product label for WAYLIVRA will require periodic blood monitoring. In each case, these label requirements could negatively affect our ability to attract and retain patients for these medicines. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help manage these safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. While we believe we and Akcea can better maintain patients on TEGSEDI and WAYLIVRA through patient-centric commercial approaches where we plan to have greater involvement with physicians and patients, if we cannot effectively maintain patients on TEGSEDI or WAYLIVRA, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

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

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

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

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

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

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

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of products in our development pipeline. For example, Zolgensma (AVXS-101), Risdiplam (RG7916), Reldesemtiv and Firdapse could compete with SPINRAZA, and ONPATTRO (approved in the U.S. and Europe for a similar indication as TEGSEDI), Tafamadis, AG10, CRX-1008 and Vutrisiran could compete with TEGSEDI. Also, Metreleptin and Gemcabene could compete with WAYLIVRA, while Laquinimod, OMS823, Selistat, VX15, WVE-120101 and WVE-120102 could compete with IONIS-HTT$_{Rx}$.

Following approval, our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA could be subject to regulatory limitations.

Following approval of a medicine, 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, TEGSEDI and WAYLIVRA.

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. For example:

- In the U.S., TEGSEDI's label contains a boxed warning for thrombocytopenia and glomerulonephritis;
- TEGSEDI requires periodic blood and urine monitoring; and
- in the U.S. TEGSEDI is available only through a Risk Evaluation and Mitigation Strategy, or REMS, program.

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, TEGSEDI and WAYLIVRA.

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

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

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

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

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

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

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

To successfully commercialize TEGSEDI Akcea must successfully manage its marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. Akcea may not be successful in doing so. To commercialize TEGSEDI in the initial indications Akcea is pursuing, Akcea will need to optimize and maintain a specialty sales force in each global region it expects to market TEGSEDI, supported by case managers, reimbursement specialists, partnerships with specialty pharmacies, injection training, routine blood and urine monitoring and a medical affairs team. Akcea may seek to further penetrate markets by expanding its sales force or through strategic partnerships with other pharmaceutical or biotechnology companies or third-party sales organizations.

Even though certain members of Akcea's management team and other employees have experience commercializing drug products, Akcea has no prior experience marketing, selling or distributing drug products, and there are significant risks involved in building and managing a commercial infrastructure. It will be expensive and time consuming for Akcea to maintain its own sales force and related compliance protocols to market TEGSEDI. Akcea may never successfully optimize or manage this capability and any failure could preclude the successful commercialization of TEGSEDI. Akcea and its partners, if any, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel.

Akcea incurred expenses prior to the launch of TEGSEDI to integrate and manage the associated marketing and sales infrastructure. If regulatory requirements or other factors cause the commercial launch of TEGSEDI to be less successful than expected, Akcea will have incurred expenses for having invested in these capabilities prior to realizing any significant revenue from sales of TEGSEDI. Akcea's sales force and marketing teams may not successfully commercialize TEGSEDI.

To the extent we and Akcea decide to rely on third parties to commercialize TEGSEDI in a particular geographic market, such as the collaboration Akcea has with PTC Therapeutics to commercialize TEGSEDI in Latin America, we may receive less revenue than if Akcea commercialized TEGSEDI by itself. Further we would have less control over the sales efforts of any other third parties involved in commercializing TEGSEDI.

If Akcea cannot effectively build and manage its distribution, medical affairs, market access, marketing and sales infrastructure, or find a suitable third party to perform such functions, the commercial launch and sales of TEGSEDI 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 medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, 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 U.S. who would fit within our target patient populations for our medicines have their healthcare supported by a combination of Medicare coverage, other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new 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 medicines 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 U.S., 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 U.S. and in international markets. For example, in the U.S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several 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 medicines may not be available or adequate in either the U.S. or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

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

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

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

We cannot guarantee that any of our medicines, including WAYLIVRA, will be considered safe and effective, or will be approved for commercialization. In addition, we cannot guarantee that SPINRAZA and TEGSEDI 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 medicines 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 medicines. It is possible that regulatory agencies will not approve our medicines, including WAYLIVRA, for marketing or additional marketing authorizations for SPINRAZA or TEGSEDI. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, the agency will not approve the specific medicine or will require additional studies, which can be time consuming and expensive and which will delay or harm commercialization of the medicine. For example, Akcea received a CRL from the FDA and a preliminary notice of noncompliance withdrawal letter from Health Canada for WAYLIVRA. As result, Akcea may need to submit additional data to the FDA and Health Canada or conduct additional clinical studies before obtaining marketing authorization, which would be expensive and cause delays. The CHMP of the EMA has adopted a positive opinion recommending conditional marketing authorization of WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion will now be referred to the EC, which grants marketing authorization for medicines in the European Union, as well as to European Economic Area members Iceland, Liechtenstein and Norway, however, the EC may decide not to adopt the CHMP's positive opinion.

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

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

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our medicines 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 medicines that have not met the primary clinical end points in their Phase 3 studies. Similar results could occur in clinical studies for our medicines, including the study of WAYLIVRA in patients with FPL and the study of IONIS-HTT_{Rx} in patients with Huntington's disease. If any of our medicines in clinical studies, including WAYLIVRA and IONIS-HTT_{Rx}, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

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

Successful results in preclinical or initial human clinical studies, including the Phase 2 results for some of our medicines in development, may not predict the results of subsequent clinical studies, including the Phase 3 study of WAYLIVRA in patients with FPL and the pivotal study of IONIS-HTT_{Rx} in patients with Huntington's disease. There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a medicine on subjects in the trial;
- we 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 medicines or other materials necessary to conduct our clinical studies may be insufficient, inadequate or delayed.

In addition, our current medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could have, or be perceived by a regulatory authority to have, an impact on a different 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 medicines or increase our costs. For example, the FDA or other regulatory agencies could request, among other things, any of the following regarding one of our medicines: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. Similarly, we have an ongoing Phase 3 study of WAYLIVRA in patients with FPL, an ongoing open-label extension study of WAYLIVRA in patients with FCS, an ongoing open-label extension study of TEGSEDI and expanded access programs for each medicine. Adverse events or results from these studies could negatively impact our current or planned marketing approval applications for WAYLIVRA in patients with FCS or the commercial opportunity for each product.

Any failure or delay in the clinical studies, including the Phase 3 study for WAYLIVRA in patients with FPL and the pivotal study of IONIS-HTT_{Rx} in patients with Huntington's disease, could reduce the commercial potential or viability of our medicines.

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

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

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. We 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 medicines, including authorizations for SPINRAZA, TEGSEDI and WAYLIVRA, or result in enforcement action after authorization that could limit the commercial success of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA.

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

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

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 historically exceeded our revenue since we were founded in January 1989. As of December 31, 2018, we had an accumulated deficit of approximately $1.0 billion and stockholders' equity of approximately $1,187.2 million. Most of our historical losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our income has come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. If we do not continue to earn substantial revenue, we may incur additional operating losses in the future. We may not successfully develop any additional products or achieve or sustain future profitability.

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

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

Under the Tax Cut and Jobs Act of 2017, or the Tax Act, federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the deductibility of such federal net operating losses is limited. It is uncertain if and to what extent various states will conform to the 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. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our net operating loss carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations.

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

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

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

Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. For example, as part of a reprioritization of its pipeline and strategic review of its rare disease business, GSK declined its option on TEGSEDI and IONIS-FB-L_{Rx}.

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

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

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

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

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

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

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, TEGSEDI and WAYLIVRA, 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 U.S. 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 parties may successfully challenge, invalidate or circumvent our issued patents or patents licensed to us so that our patent rights do not create an effective competitive barrier or revenue source.

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 U.S. 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.

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

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

Many of our medicines are undergoing clinical studies or are in the early stages of research and development. Most of our drug programs will require significant additional research, development, preclinical and/or clinical testing, marketing authorization and/or commitment of significant additional resources prior to their successful commercialization. As of December 31, 2018, we had cash, cash equivalents and short-term investments equal to $2.1 billion. If we do not meet our goals to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or to license our medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

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

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

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

In January 2020, Dr. Crooke, our founder and Chief Executive Officer, plans to transition from Chief Executive Officer to Executive Chairman of our Board of Directors. As Executive Chairman, Dr. Crooke will continue to be responsible for the activities of the board and will remain active in the company, providing strategic advice and continuing to participate in the scientific activities. Our board has selected Dr. Monia, who has been our Chief Operating Officer for the last year and a member of our team since our founding nearly 30 years ago, to serve as our Chief Executive Officer starting in January 2020. If this transition is not successful, our business could suffer.

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

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

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, 2018, the market price of our common stock ranged from $59.81 to $39.07 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 medicines 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, TEGSEDI and WAYLIVRA. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, product liability claims may result in decreased demand for our 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.

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

We manufacture our research and clinical supplies in a manufacturing facility located in Carlsbad, California. We manufacture the finished drug product for TEGSEDI and WAYLIVRA at third-party contract manufacturers. The facilities and the equipment we and our contract manufacturers use to research, develop and manufacture our medicines would be costly to replace and could require substantial lead time to repair or replace. Our facilities or 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.

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.

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

A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us. For example, the Tax Act represented a substantial change to tax laws in the U.S. However, it did not have a material impact on our financial statements because we maintained a valuation allowance on all of our net operating losses and other deferred tax assets as of December 31, 2017. Over the next several years we expect to utilize our net operating losses and other deferred tax assets, and any future changes in tax laws could have a material effect on our business.

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.

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

We are dependent upon our own or third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity. Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and/or result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 20, 2019, 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	Boston, MA	30,175	Leased	2028	One, five-year option to extend
Akcea office and Ionis storage space facility	Carlsbad, CA	18,700	Leased	2023	One, five-year option to extend
		279,375			

Item 3. Legal Proceedings

Gilead Litigation

In August 2013, Gilead Sciences Inc. filed a suit in the U.S. District Court of Northern District of California related to U.S. 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 10 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. In April 2018, the Court of Appeals issued its ruling affirming the District Court's finding of unenforceability based on unclean hands. Having upheld the ruling that the patents are unenforceable against Gilead, the court did not reach the question of validity. In September 2018, we filed a petition requesting a hearing before the Supreme Court, asserting that it was improper for the trial court to overturn the jury verdict on the basis of the equitable defense of unclean hands. In January 2019, the Supreme Court denied our petition. Under our agreement with Merck, Merck is responsible for the costs of this suit.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

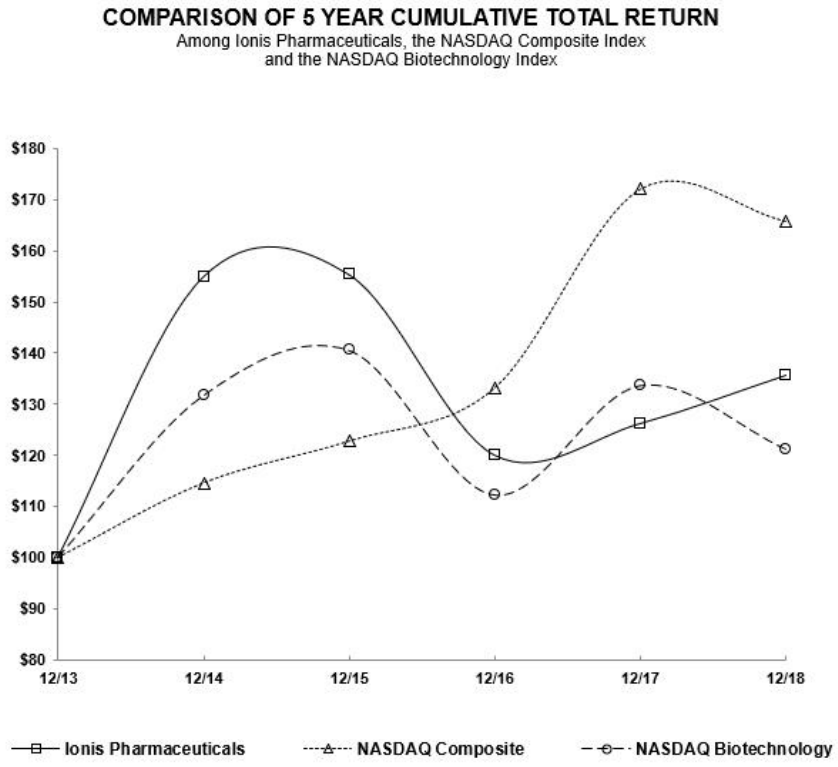
Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol "IONS." As of February 20, 2019, there were approximately 541 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, 2013 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, 2013 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-13	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18
Ionis Pharmaceuticals, Inc.	$ 100.00	$ 154.97	$ 155.45	$ 120.06	$ 126.26	$ 135.69
Nasdaq Composite Index	$ 100.00	$ 114.62	$ 122.81	$ 133.19	$ 172.11	$ 165.84
Nasdaq Biotechnology Index	$ 100.00	$ 131.71	$ 140.56	$ 112.25	$ 133.67	$ 121.24

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

Item 6. Selected Financial Data

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

	Years Ended December 31,				
	2018	2017 (1)	2016 (1)	2015	2014
Consolidated Statement of Operations Data:					
Revenue	$ 599.7	$ 514.2	$ 372.8	$ 283.7	$ 214.2
Research, development and patent expenses	$ 414.6	$ 374.6	$ 344.3	$ 322.3	$ 241.8
Selling, general and administrative expenses	$ 244.6	$ 108.5	$ 48.6	$ 37.2	$ 20.1
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 273.7	$ 0.3	$ (60.4)	$ (88.3)	$ (39.0)
Basic net income (loss) per share attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 2.09	$ 0.15	$ (0.50)	$ (0.74)	$ (0.33)
Diluted net income (loss) per share attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 2.07	$ 0.15	$ (0.50)	$ (0.74)	$ (0.33)
Shares used in computing basic net income (loss) per share	132.3	124.0	120.9	119.7	117.7
Shares used in computing diluted net income (loss) per share	134.1	126.1	120.9	119.7	117.7

	As of December 31,				
	2018	2017 (1)	2016	2015	2014
Consolidated Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 2,084.1	$ 1,022.7	$ 665.2	$ 779.2	$ 728.8
Working capital	$ 1,927.6	$ 925.1	$ 664.1	$ 688.1	$ 721.3
Total assets	$ 2,667.8	$ 1,322.8	$ 912.5	$ 947.9	$ 946.5
Long-term debt and other obligations, less current portion	$ 1,200.3	$ 713.9	$ 679.1	$ 598.2	$ 588.9
Accumulated deficit	$ (967.3)	$ (1,241.0)	$ (1,181.4)	$ (1,094.9)	$ (1,006.6)
Stockholders' equity	$ 1,187.2	$ 365.3	$ 99.6	$ 200.8	$ 257.8

(1) Reflects the impact of our adoption of the new revenue recognition accounting standard in 2018 (Topic 606). For additional details about our adoption of Topic 606, see Note 1, *Organization and Significant Accounting Policies,* in the Notes to the Consolidated Financial Statements. This change is not reflected in our consolidated statement of operations data for 2015 or 2014 or in our consolidated balance sheet data for 2016, 2015, or 2014.

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

Overview

We are a leader in discovering and developing RNA-targeted therapeutics with sustained and growing revenues. We have created an efficient and broadly applicable drug discovery platform leveraging our expertise in antisense oligonucleotide therapeutics that we believe has fundamentally changed medicine and transformed the lives of people with devastating and often deadly diseases. Our large, diverse and advanced pipeline of over 40 first-in-class and/or best-in-class medicines addresses diseases across a broad range of therapeutic areas, targeting small, medium and large patient populations.

We have two commercial medicines approved in major markets around the world, SPINRAZA and TEGSEDI. We have at least four medicines that have entered pivotal studies or have the potential to begin pivotal studies this year, and another six medicines that could start pivotal studies in 2020. These medicines, along with the more than 30 additional medicines in our pipeline, represent multiple potential drivers of value for years to come. We believe our efficient drug discovery platform, coupled with our innovation-centric business model, provides us with the flexibility to determine the optimal development and commercialization strategy to maximize the commercial opportunity for each of our medicines and ensure that we continue to produce transformative medicines for patients who need them. We believe we are positioned to drive substantial value for patients and shareholders.

As of January 2019, SPINRAZA was approved in over 40 countries around the world, and our partner Biogen, who is responsible for global SPINRAZA commercial activities, reported that more than 6,600 patients are now on SPINRAZA therapy. In addition, Biogen plans to continue to pursue regulatory filings in additional countries. Biogen reported 2018 annual sales of SPINRAZA of more than $1.7 billion, and we earned $238 million in commercial revenues from royalties on sales of SPINRAZA. SPINRAZA is the first and only approved medicine for the treatment of SMA. SPINRAZA is the established standard-of-care for all people with this progressive, debilitating and often fatal genetic disease. In November 2018, SPINRAZA was recognized with the 2018 International Prix Galien award as Best Biotechnology Product. This prestigious honor marks the seventh Prix Galien award for SPINRAZA.

TEGSEDI, a once weekly, self-administered subcutaneous medicine, was approved in 2018 in the U.S., EU and Canada for the treatment of polyneuropathy caused by hATTR in adult patients. hATTR is a debilitating, progressive, and fatal disease. Akcea, our majority-owned affiliate focused on developing and commercializing medicines to treat patients with rare and serious diseases, launched TEGSEDI globally in late 2018. In the fourth quarter of 2018, we earned more than $2 million in TEGSEDI product sales. Akcea has an exclusive license agreement with PTC to commercialize TEGSEDI in Latin America. In January 2019, PTC filed an application for regulatory approval in Brazil with ANVISA, the Brazilian regulatory authority. ANVISA granted priority review for TEGSEDI.

We and Akcea are preparing to commercialize WAYLIVRA in the EU. The CHMP of the EMA adopted a positive opinion recommending conditional marketing authorization for WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion will now be referred to the EC which grants marketing authorization for medicines in the EU, as well as to European Economic Area members Iceland, Liechtenstein and Norway. With this positive opinion, and, pending adoption of the positive opinion by the EC, Akcea plans to leverage its existing commercial infrastructure in Europe to market WAYLIVRA. Akcea is continuing to conduct open-label extension and early access programs. We are also focused on regulatory discussions in the U.S. We are developing WAYLIVRA to treat FPL a second severe and rare, genetically defined disease. 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.

In addition to commercializing TEGSEDI and preparing to commercialize WAYLIVRA, Akcea is developing four other clinical-stage medicines: AKCEA-APO(a)-L_{Rx} (TQJ230), AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-TTR-L_{Rx}, each of which could potentially treat multiple patient populations. Moving these drugs into Akcea allows us to retain substantial value from these medicines and ensures our core focus remains on innovation. As of February 2019, we owned approximately 75 percent of Akcea.

We are continuously advancing our technology and pipeline to provide the most value to patients. We have a pipeline of over 40 medicines that, like SPINRAZA and TEGSEDI, have the potential to transform the treatment of diseases with no adequate treatment today. These medicines range from treatments for rare diseases with small patient populations to more common diseases afflicting millions of patients. Our pipeline covers a broad spectrum of therapeutic areas, such as cardiometabolic diseases, neurodegenerative diseases, cancer, severe and rare diseases and others. We believe our large and diverse pipeline contains many near-, mid- and longer-term growth drivers for the company.

Our pipeline includes at least 10 potentially transformative medicines anticipated to enter pivotal clinical studies in the next two years. We anticipate at least four of these medicines will enter pivotal studies this year including: AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, IONIS-HTT_{Rx} (RG6042) and IONIS-$SOD1_{Rx}$. Roche recently initiated a Phase 3 study of IONIS-HTT_{Rx} for HD. We believe each of these medicines is a first-in-class and/or best-in-class medicine with the potential to deliver significant value to patients and shareholders. We anticipate that the data from these pivotal studies, if positive, will support global regulatory filings for each medicine.

The depth of our knowledge and expertise with antisense technology together with our strong financial position provides us the flexibility to partner our medicines at what we believe is the optimal time to maximize the near-term, mid-term and long-term value of our medicines. We have a distinct partnering strategy based on each specific medicine and the expertise and resources we and our potential partners may bring to a collaboration. We may develop and commercialize some medicines through affiliates. In general, these are medicines, like TEGSEDI, that can benefit from our internal expertise and infrastructure, have manageable development costs and have the potential for initial rare disease indications. For other medicines, we may establish collaborations to advance the medicine. We have alliances with a cadre of leading global pharmaceutical companies that are working alongside us in developing our medicines, advancing our technology, preparing to commercialize our medicines and selling our medicines. Our partners include the following companies, among others: AstraZeneca, Bayer, Biogen, GSK, Janssen, Novartis and Roche. Our partners bring resources and expertise that augment and build upon our internal capabilities. We have the potential to earn over $20 billion in future milestone payments and licensing fees from our existing partnerships.

Financial Highlights

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

	Years Ended December 31,		
	2018	2017	2016
		(as revised)	
Total revenue	$ 599,674	$ 514,179	$ 372,776
Total operating expenses	$ 661,046	$ 483,132	$ 392,936
Income (loss) from operations	$ (61,372)	$ 31,047	$ (20,160)
Net income (loss)	$ 214,985	$ (10,783)	$ (60,400)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 273,741	$ 346	$ (60,400)
Cash, cash equivalents and short-term investments	$ 2,084,072	$ 1,022,715	$ 665,223

Our revenue for 2018 was $599.7 million and increased significantly compared to 2017 and 2016, primarily from increased commercial revenue from SPINRAZA royalties.

Our operating expenses for 2018 were $661.0 million and continued to increase year-over-year. The increase in operating expenses was primarily due to higher SG&A expenses as we prepared to commercialize TEGSEDI and WAYLIVRA. Our SG&A expenses also increased because of fees we owed under our in-licensing agreements related to SPINRAZA. We earn tiered royalties on annual SPINRAZA sales and pay nominal fixed third-party royalties that are not tiered. R&D expenses accounted for a smaller portion of the increase in operating expenses.

The increase in 2018 net income attributable to Ionis' common stockholders was primarily due to increases in revenue and the income tax benefit we recognized in the fourth quarter of 2018. Our tax benefit increased significantly in 2018 primarily due to a one-time non-cash tax benefit related to Ionis' stand-alone deferred federal income tax assets. In the fourth quarter of 2018, we released a large portion of our valuation allowance associated with our deferred tax assets. As a result of our strong financial performance over the past few years and our outlook regarding the continued growth of our business, we determined that it was more likely than not that we would be able to realize most of our deferred income tax assets we have accumulated to offset future taxable income.

During 2018 we received more than $1.5 billion in payments from our partners, including $1 billion from Biogen for our 2018 strategic neurology collaboration. This is compared to $580 million received in 2017 and $190 million received in 2016. We believe our strong financial position should enable us to continue to execute on our corporate goals throughout 2019 and beyond.

Business Segments

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

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;
- Valuing premiums received under our collaborations;
- Determining the proper valuation of investments in marketable securities;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- ncome taxes.

Descriptions of these critical accounting policies follow.

Revenue Recognition

Adoption of New Revenue Recognition Accounting Standard (Topic 606)

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. This guidance supersedes the revenue recognition requirements we previously followed in Accounting Standards Codification, or ASC, Topic 605, *Revenue Recognition*, or Topic 605, and created a new Topic 606, *Revenue from Contracts with Customers*, or Topic 606. Under Topic 606, 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. We adopted Topic 606 on January 1, 2018 under the full retrospective approach, which required us to revise our prior period revenue. Under Topic 606, we were required to review all of our ongoing collaboration agreements in which we recognized revenue after January 1, 2016. We were required to assess what our revenue would have been for the period from January 1, 2016 to December 31, 2017 under Topic 606. As a result of this analysis, we determined that the cumulative revenue we would have recognized under Topic 606 decreased by $86.1 million. We recorded this amount as a cumulative adjustment to our accumulated deficit as of January 1, 2016 on our revised statement of stockholders' equity. We have labeled our prior period financial statements "as revised" to indicate the change required under the accounting rules.

The following tables summarize the adjustments we were required to make to amounts we originally reported in 2017 and 2016 to adopt Topic 606 (in thousands, except per share amounts):

Consolidated Balance Sheet

	At December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Current portion of deferred contract revenue	$ 106,465	$ 18,871	$ 125,336
Long-term portion of deferred contract revenue	$ 72,708	$ 35,318	$ 108,026
Accumulated deficit	$ (1,187,398)	$ (53,636)	$ (1,241,034)
Noncontrolling interest in Akcea Therapeutics, Inc.	$ 87,847	$ (3,580)	$ 84,267
Total stockholders' equity	$ 418,719	$ (53,439)	$ 365,280

Consolidated Statements of Operations

	Year Ended December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 112,540	$ —	$ 112,540
Licensing and other royalty revenue	9,519	(2,045)	7,474
Total commercial revenue	122,059	(2,045)	120,014
Research and development revenue under collaborative agreements	385,607	8,558	394,165
Total revenue	$ 507,666	$ 6,513	$ 514,179
Income from operations	$ 24,534	$ 6,513	$ 31,047
Net income (loss)	$ (17,296)	$ 6,513	$ (10,783)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (5,970)	$ 6,316	$ 346
Net income per share, basic and diluted	$ 0.08	$ 0.07	$ 0.15

	Year Ended December 31, 2016		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 883	$ —	$ 883
Licensing and other royalty revenue	19,839	2,045	21,884
Total commercial revenue	20,722	2,045	22,767
Research and development revenue under collaborative agreements	325,898	24,111	350,009
Total revenue	$ 346,620	$ 26,156	$ 372,776
Income (loss) from operations	$ (46,316)	$ 26,156	$ (20,160)
Net income (loss)	$ (86,556)	$ 26,156	$ (60,400)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (86,556)	$ 26,156	$ (60,400)
Net income (loss) per share, basic and diluted	$ (0.72)	$ 0.22	$ (0.50)

Consolidated Statements of Cash Flows

	Year Ended December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Net income (loss)	$ (17,296)	$ 6,513	$ (10,783)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Deferred contract revenue	$ 36,695	$ (6,513)	$ 30,182
Cash and cash equivalents at beginning of period	$ 84,685	$ —	$ 84,685
Cash and cash equivalents at end of period	$ 129,630	$ —	$ 129,630

	Year Ended December 31, 2016		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Net income (loss)	$ (86,556)	$ 26,156	$ (60,400)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Deferred contract revenue	$ (59,150)	$ (26,156)	$ (85,306)
Cash and cash equivalents at beginning of period	$ 128,797	$ —	$ 128,797
Cash and cash equivalents at end of period	$ 84,685	$ —	$ 84,685

Under Topic 606, compared to Topic 605, our total revenue increased $6.5 million for 2017 and $26.2 million for 2016. The change in our revenue was primarily due to:

- A change in how we recognize milestone payments: Topic 606 requires us to amortize more of the milestone payments we achieve, rather than recognizing the milestone payments in full in the period in which we achieved the milestone event as we did under Topic 605. This change resulted in an increase in R&D revenue recognized for 2017 and 2016 of $23.6 million and $24.1 million, respectively.

- A change in how we calculate revenue for payments we are recognizing into revenue over time: Under Topic 605, we amortized payments into revenue evenly over the period of our obligations. When we made a change to our estimated completion period, we recognized that change on a prospective basis. Under Topic 606, we use an input method to determine the amount we amortize each reporting period. Each period, we review our "inputs" such as our level of effort expended, including the time we estimate it will take us to complete the activities, or costs incurred relative to the total expected inputs to satisfy the performance obligation. For certain collaborations, such as Bayer, Janssen and Novartis, the input method resulted in a change to the revenue we had previously recognized using a straight-line amortization method. This change resulted in a decrease in our R&D revenue of $15.1 million for 2017. This change did not result in an impact to our 2016 R&D revenue.

Our updated revenue recognition policy reflecting Topic 606 is as follows:

Our Revenue Sources

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

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

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

Commercial Revenue: TEGSEDI product sales, net

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

Research and development revenue under collaborative agreements

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

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

Steps to Recognize Revenue

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

1. Identify the contract

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

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

2. Identify the performance obligations

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

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

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

3. Determine the transaction price

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

Milestone payments are our most common type of variable consideration. We recognize milestone payments using the most likely amount method because we will either receive the milestone payment or we will not, which makes the potential milestone payment a binary event. The most likely amount method requires us to determine the likelihood of earning the milestone payment. We include a milestone payment in the transaction price once it is probable we will achieve the milestone event. Most often, we do not consider our milestone payments probable until we or our partner achieve the milestone event because the majority of our milestone payments are contingent upon events that are not within our control and are usually based on scientific progress. For example, in January 2019 we earned a $35 million milestone payment from Roche when it dosed the first patient in the Phase 3 study of IONIS-HTT$_{Rx}$. At December 31, 2018, we determined it was not probable that we could earn this milestone payment. As such, we did not recognize any revenue associated with it in 2018.

4. Allocate the transaction price

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

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

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

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

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

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

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

5. Recognize revenue

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

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

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

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We recognize royalty revenue in the period in which the counterparty sells the related product, which in certain cases may require us to estimate our royalty revenue. We recognize royalties from SPINRAZA sales in the period Biogen records the sale of SPINRAZA. Our accounting for SPINRAZA royalties did not change as a result of adopting Topic 606.

Commercial Revenue: TEGSEDI Product Sales, net

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

Reserves for TEGSEDI Product Sales

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

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

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

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

Trade discounts and allowances: We provide customary invoice discounts on TEGSEDI product sales to our U.S. customer for prompt payment. We record this discount as a reduction of TEGSEDI product sales in the period in which we recognize the related product revenue. In addition, we receive and pay for various distribution services from our U.S. customer and wholesalers in our U.S. distribution channel. For services we receive that are either not distinct from the sale of TEGSEDI or for which we cannot reasonably estimate the fair value, we classify such fees as a reduction of TEGSEDI product sales.

Product Returns: Our U.S. customer has return rights and the wholesalers have limited return rights primarily related to the expiration date of the TEGSEDI product. We estimate the amount of TEGSEDI product sales that our customer may return. We record our return estimate as an accrued refund liability on our consolidated balance sheet with a corresponding offset reducing our TEGSEDI product sales, in the same period we recognize the related sale. Based on our distribution model for TEGSEDI, contractual inventory limits with our customer and wholesalers and the price of TEGSEDI, we believe we will have minimal returns. Our customer in Germany only takes title to the product once it receives an order from a hospital or pharmacy and therefore does not maintain any inventory of TEGSEDI, as such we do not estimate returns in Germany.

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

Research and development revenue under collaboration agreements:

Upfront Payments

When we enter into a collaboration agreement with an upfront payment, we typically record the entire upfront payment as deferred revenue if our only performance obligation is for R&D services we will provide in the future. We amortize the upfront payment into revenue as we perform the R&D services. For example, under our new collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases, we received a $75 million upfront payment in the fourth quarter of 2018. We allocated the upfront payment to our single performance obligation, R&D services. We are amortizing the $75 million upfront payment using an input method over the estimated period of time we are providing R&D services. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion. Under Topic 605, we amortized upfront payments evenly over the period of our obligation.

Milestone Payments

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

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, in the third quarter of 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. Under Topic 606, we added this payment to the transaction price and allocated it to our R&D services performance obligation. We are recognizing revenue from this milestone payment over our estimated period of performance. Under Topic 605, this milestone payment was recognized in full in the third quarter of 2017, which was the period in which we achieved the milestone event.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event. For example, in the third quarter of 2018, we recognized a $10 million milestone payment when AstraZeneca initiated a Phase 1 study of IONIS-AZ4-2.5-L_{Rx}. We concluded that the milestone payment was not related to our R&D services performance obligation. Therefore, we recognized this milestone payment in full in the third quarter of 2018 because we do not have any performance obligations related to this milestone payment. Our revenue recognition of milestone payments we earn based on our partners' activities did not change as a result of adopting Topic 606.

License Fees

We generally recognize as revenue the total amount we determine to be the stand-alone selling price of a license when we deliver the license to our partner. This is because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery. For example, in the fourth quarter of 2018, we earned a $35 million license fee when Biogen licensed IONIS-SOD1$_{Rx}$ from us. Our recognition of license fees did not change as a result of adopting Topic 606.

Amendments to Agreements

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

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

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

For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. As part of the agreement, Bayer paid us a $100 million upfront payment. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis and for providing an initial supply of API. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. As part of the 2017 amendment, Bayer paid us $75 million. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$ and IONIS-FXI-L$_{Rx}$. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of IONIS-FXI-L$_{Rx}$, to provide R&D services and to deliver API. We allocated the $75 million transaction price to these performance obligations. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion of our accounting treatment for our Bayer collaboration. Our allocation of the consideration we received for the Bayer amendment did not change as a result of adopting Topic 606. However, the method in which we are recognizing revenue related to our R&D services performance obligation did change. We are amortizing revenue related to our R&D services performance obligation using the input method under Topic 606.

Multiple Agreements

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

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

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

For example, in the second quarter of 2018, we entered into two separate agreements with Biogen at the same time: a new strategic neurology collaboration agreement and a SPA. We evaluated the Biogen agreements to determine whether we should treat the agreements separately or combine them. We considered that the agreements were negotiated concurrently and in contemplation of one another. Based on these facts and circumstances, we concluded that we should evaluate the provisions of the agreements on a combined basis. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements* for further discussion of the accounting treatment for the 2018 strategic neurology collaboration with Biogen.

Deferred Revenue

We are often entitled to bill our customers and receive payment from our customers in advance of our obligation to provide services or transfer goods to our partners. In these instances, we include the amounts in deferred revenue on our consolidated balance sheet.

The following table summarizes the adjustments we were required to make to our deferred revenue amounts to adopt Topic 606 (in thousands):

	At December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Current portion of deferred revenue	$ 106,465	$ 18,871	$ 125,336
Long-term portion of deferred revenue	72,708	35,318	108,026
Total deferred revenue	$ 179,173	$ 54,189	$ 233,362

Our deferred revenue balance increased $54.2 million at December 31, 2017 under Topic 606, compared to Topic 605. The increase was primarily related to the change in the accounting for certain milestone payments and the way in which we amortize payments. Under Topic 605, we previously recognized the majority of the milestone payments we earned in the period we achieved the milestone event, which did not impact our deferred revenue balance. Under Topic 606 we are now amortizing more milestone payments over the period of our performance obligation, which adds to our deferred revenue balance. Additionally, under Topic 605 we amortized payments evenly over the period of our obligation. Under Topic 606, we use an input method to determine the amount we amortize each reporting period. The increase in deferred revenue relates to agreements with the following partners:

- $24.2 million from Biogen;
- $15.9 million from AstraZeneca;
- $11.8 million from Novartis; and
- $ 2.3 million from other partners.

Valuation of Premiums under our Collaborations

In conjunction with our collaboration agreements we have sold stock at a premium to our partners, including under our 2018 strategic neurology collaboration with Biogen and with Novartis in 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.

Biogen Premium

In the second quarter of 2018, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at a 25 percent cash premium and $375 million in an upfront payment. At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined the transaction price to be $552 million, comprised of $375 million from the upfront payment and $177 million for the premium paid by Biogen for its purchase of our common stock. We determined the fair value of the premium we received by using the stated premium in the SPA and applying a lack of marketability discount. We included a lack of marketability discount in our valuation of the premium because Biogen received restricted shares.

Novartis Premiums

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.

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 medicines 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.

Income Taxes

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

For U.S. federal income tax purposes we are required to file separate U.S. federal income tax returns for Ionis and Akcea. We began deconsolidating Akcea for U.S. federal income tax purposes upon Akcea's initial public offering. As a result, we are required to assess Ionis' stand-alone and Akcea's valuation allowances separately even though we consolidate Akcea's financial results in our consolidated financial statements. We continue to file combined state tax returns in most jurisdictions. As a result, we continue to assess the state portion of our valuation allowance for those jurisdictions on a consolidated basis.

We have historically recorded a valuation allowance against all our net deferred tax assets due to cumulative financial statement losses. However, in the fourth quarter of 2018, we reversed the valuation allowance previously recorded against Ionis' stand-alone U.S. federal net deferred tax assets, resulting in a one-time non-cash tax benefit of $332.1 million. Given our current stand-alone Ionis pre-tax income, and assuming we maintain this current level of Ionis stand-alone pre-tax income, we expect to generate income before taxes in the U.S. in future periods at a level that would result in us fully utilizing our U.S. federal net operating loss carryforwards and most of our existing Research and Development and Orphan Drug tax credit carryforwards over the next three years.

We continue to maintain a full valuation allowance of $234.2 million against all of Akcea's net deferred tax assets and the net state deferred tax assets of Ionis at December 31, 2018 due to uncertainties related to our ability to realize the tax benefits associated with these assets.

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

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

Results of Operations

Whenever we refer to prior period results, they reflect the impact of Topic 606, which we adopted in the first quarter of 2018.

Years Ended December 31, 2018 and December 31, 2017

Revenue

Total revenue for 2018 was $599.7 million, compared to $514.2 million in 2017 and was comprised of the following (amounts in thousands):

	Year Ended December 31,	
	2018	2017 (as revised)
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 237,930	$ 112,540
TEGSEDI product sales, net	2,237	—
Licensing and other royalty revenue	14,755	7,474
Total commercial revenue	254,922	120,014
R&D revenue:		
Amortization from upfront payments	124,695	97,646
Milestone payments	82,771	152,008
License fees	102,053	116,095
Other services	35,233	28,416
Total R&D revenue	344,752	394,165
Total revenue	$ 599,674	$ 514,179

The increase in revenue in 2018 compared to 2017 was primarily due to increasing commercial revenue from SPINRAZA royalties, which more than doubled. We added TEGSEDI product sales in the fourth quarter of 2018. Additionally, we more than doubled our licensing and royalty revenue in 2018 compared to 2017, primarily from the license fee we earned from PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America.

R&D revenue from the amortization of upfront payments increased over $25 million in 2018 compared to 2017. The increase in amortization was primarily due to our 2018 strategic neurology collaboration with Biogen. Additionally, we added amortization revenue from our new collaboration with Roche to develop IONIS-FB-L_{Rx} in 2018. Our R&D revenue from milestone payments, license fees and other services continued to make a significant contribution to our financial results.

Already in the first quarter of 2019, we have earned $185 million. We earned $150 million from Novartis when it licensed AKCEA-APO(a)-L_{Rx} and $35 million from Roche when it dosed the first patient in the Phase 3 study of IONIS-HTT_{Rx} in patients with Huntington's disease.

Operating Expenses

Operating expenses for 2018 were $661.0 million, and increased compared to $483.1 million for 2017. Our operating expenses increased year over year principally due to higher SG&A expenses as we prepared to commercialize TEGSEDI and WAYLIVRA. Our SG&A expenses also increased year over year because of fees we owed under our in-licensing agreements related to SPINRAZA. We earn tiered royalties on annual SPINRAZA sales and pay nominal fixed third-party royalties that are not tiered. R&D expenses accounted for a smaller portion of the increase in operating expenses. R&D expenses for 2018 increased compared to 2017 primarily due to increases in drug development costs related to several medicines, including AKCEA-APOCIII-L_{Rx}, as we, with Akcea, advanced these programs in development. These increases reflect the investment we are making in advancing and expanding our pipeline.

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

	Year Ended December 31,	
	2018	2017
Ionis Core	$ 293,175	$ 305,352
Akcea Therapeutics	251,408	146,332
Elimination of intercompany activity	(14,849)	(54,527)
Subtotal	529,734	397,157
Non-cash compensation expense related to equity awards	131,312	85,975
Total operating expenses	$ 661,046	$ 483,132

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.

Cost of Products Sold

Our cost of products sold consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TEGSEDI, certain associated period costs. We not expect our fixed costs will increase in direct correlation to TEGSEDI product sales. We expensed a significant portion of the cost of producing TEGSEDI that Akcea is using in the commercial launch as R&D expense prior to the regulatory approval of TEGSEDI. We expect cost of products sold to increase as we deplete these inventories.

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

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

For 2018, our cost of products sold was $1.7 million. We began recognizing cost of products sold in 2018 when TEGSEDI was approved. We previously recognized $0.1 million of costs to produce TEGSEDI related to the TEGSEDI commercial revenue we recognized in 2018 because we incurred these costs before we obtained regulatory approval. We did not have cost of products sold in 2017. Akcea includes the amortization for milestone payments it made to us related to the U.S. and European approvals of TEGSEDI in its cost of products sold. Akcea is recognizing this amortization over TEGSEDI's remaining estimated patent life. This amortization is eliminated in our consolidated results. All amounts exclude non-cash compensation expense related to equity awards.

Research, Development and Patent Expenses

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

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

	Year Ended December 31,	
	2018	2017
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 338,047	$ 310,123
Non-cash compensation expense related to equity awards	76,557	64,521
Total research, development and patent expenses	$ 414,604	$ 374,644

For 2018, our research, development and patent expenses were $338.0 million, compared to $310.1 million for 2017. The increase in our R&D expenses for 2018, compared to 2017 was driven primarily by increases in drug development costs related to several medicines including AKCEA-APOCIII-L_{Rx} and AKCEA-ANGPTL3-L_{Rx}, as we advanced these programs in development. 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,	
	2018	2017
Ionis Core	$ 222,528	$ 246,390
Akcea Therapeutics	120,905	118,260
Elimination of intercompany activity	(5,386)	(54,527)
Subtotal	338,047	310,123
Non-cash compensation expense related to equity awards	76,557	64,521
Total research, development and patent expenses	$ 414,604	$ 374,644

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. Our antisense drug discovery expenses are part of our Ionis Core business segment.

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

	Year Ended December 31,	
	2018	2017
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 61,387	$ 56,160
Non-cash compensation expense related to equity awards	17,530	15,203
Total antisense drug discovery expenses	$ 78,917	$ 71,363

Antisense drug discovery expenses for 2018 were $61.4 million and were slightly higher compared to $56.2 million for 2017 due to an increase in expenses we incurred in 2018 related to our expanding early stage research programs. All amounts exclude non-cash compensation expense related to equity awards.

Antisense Drug Development

The following table sets forth drug development expenses, including the breakdown for medicines in Phase 3 development and/or commercialization for which we have incurred significant costs (in thousands):

	Year Ended December 31,	
	2018	2017
SPINRAZA	$ —	$ 10,996
WAYLIVRA	19,397	22,524
TEGSEDI	19,204	24,880
Other antisense development projects	116,936	79,106
Development overhead expenses	48,754	43,784
Total antisense drug development, excluding non-cash compensation expense related to equity awards	204,291	181,290
Non-cash compensation expense related to equity awards	34,845	28,325
Total antisense drug development expenses	$ 239,136	$ 209,615

Antisense drug development expenses were $204.3 million for 2018 and increased compared to $181.3 million for 2017. During 2018, our development expenses for AKCEA-APOCIII-L_{Rx} and AKCEA-ANGPTL3-L_{Rx} increased compared to 2017. We completed enrollment of the Phase 2 clinical study of AKCEA-APO(a)-L_{Rx} during the first quarter of 2018 and reported positive Phase 2 data in the third quarter of 2018. We also initiated a Phase 2 clinical study of AKCEA-APOCIII-L_{Rx} in patients with hypertriglyceridemia and established cardiovascular disease in the first quarter of 2018. Slightly offsetting these increases were decreased expenses for SPINRAZA, TEGSEDI and WAYLIVRA. Specifically, we have transitioned all further development of SPINRAZA to Biogen. In early 2017, we completed our Phase 3 WAYLIVRA trial in patients with FCS and our Phase 3 TEGSEDI trial in patients with hATTR with polyneuropathy. 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,	
	2018	2017
Ionis Core	$ 100,090	$ 123,934
Akcea Therapeutics	104,201	105,751
Elimination of intercompany activity	—	(48,395)
Subtotal	204,291	181,290
Non-cash compensation expense related to equity awards	34,845	28,325
Total antisense drug development expenses	$ 239,136	$ 209,615

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 medicines 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.

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,	
	2018	2017
Manufacturing and operations expenses, excluding non-cash compensation expense related to equity awards	$ 39,806	$ 43,526
Non-cash compensation expense related to equity awards	9,036	6,904
Total manufacturing and operations expenses	$ 48,842	$ 50,430

Manufacturing and operations expenses were $39.8 million for 2018 and declined slightly compared to $43.5 million for 2017. 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,	
	2018	2017
Ionis Core	$ 32,277	$ 39,098
Akcea Therapeutics	12,758	10,440
Elimination of intercompany activity	(5,229)	(6,012)
Subtotal	39,806	43,526
Non-cash compensation expense related to equity awards	9,036	6,904
Total manufacturing and operations expenses	$ 48,842	$ 50,430

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,	
	2018	2017
Personnel costs	$ 12,968	$ 11,432
Occupancy	8,567	8,236
Patent expenses	2,744	2,095
Depreciation and amortization	439	249
Insurance	1,622	1,735
Other	6,223	5,400
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	32,563	29,147
Non-cash compensation expense related to equity awards	15,146	14,089
Total R&D support expenses	$ 47,709	$ 43,236

R&D support expenses for 2018 were $32.6 million compared to $29.1 million for 2017. R&D support expenses increased slightly primarily related to costs associated with the expansion of our business. 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,	
	2018	2017
Ionis Core	$ 28,774	$ 27,198
Akcea Therapeutics	3,946	2,069
Elimination of intercompany activity	(157)	(120)
Subtotal	32,563	29,147
Non-cash compensation expense related to equity awards	15,146	14,089
Total R&D support expenses	$ 47,709	$ 43,236

Selling, General and Administrative Expenses

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

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

	Year Ended December 31,	
	2018	2017
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 190,027	$ 87,034
Non-cash compensation expense related to equity awards	54,595	21,454
Total selling, general and administrative expenses	$ 244,622	$ 108,488

Selling, general and administrative expenses were $190.0 million for 2018 and significantly increased compared to $87.0 million for 2017. The increase in SG&A expenses was principally due to the cost of preparing to commercialize TEGSEDI and WAYLIVRA, and an increase in the fees we owed under our in-licensing agreements related to SPINRAZA. We project our expenses will increase as we continue to launch TEGSEDI. 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,	
	2018	2017
Ionis Core	$ 70,647	$ 58,962
Akcea Therapeutics	118,930	28,072
Elimination of intercompany activity	450	—
Subtotal	190,027	87,034
Non-cash compensation expense related to equity awards	54,595	21,454
Total selling general and administrative expenses	$ 244,622	$ 108,488

Akcea Therapeutics, Inc.

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

	Year Ended December 31,	
	2018	2017
Cost of products sold	$ 11,573	$ —
Development and patent expenses	120,905	118,260
Selling, general and administrative expenses	118,930	28,072
Total operating expenses, excluding non-cash compensation expense related to equity awards	251,408	146,332
Non-cash compensation expense related to equity awards	44,275	17,539
Total Akcea Therapeutics operating expenses	$ 295,683	$ 163,871

Operating expenses for Akcea were $251.4 million for 2018 and increased compared to $146.3 million for 2017.

In the third quarter of 2018, Akcea began recognizing cost of products sold expenses after the approval of TEGSEDI.

In 2017, $48.4 million of 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. Excluding the $48.4 million of one-time expenses, Akcea's development and patent expenses increased $51.0 million in 2018 compared to 2017 as Akcea made investments in advancing its pipeline, including AKCEA-APO(a)-L_{Rx}, and AKCEA-APOCIII-L_{Rx}. 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 SG&A expenses increased in 2018 compared to 2017, primarily because Akcea was building its commercial infrastructure and advancing the pre-commercialization activities necessary to successfully launch TEGSEDI and WAYLIVRA. 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.

Investment Income

Investment income for 2018 was $30.2 million compared to $8.2 million for 2017. Investment income increased primarily due to a significantly higher average cash balance and to a lesser extent an improvement in the market conditions during 2018 compared to 2017.

Interest Expense

Interest expense was $44.8 million for both 2018 and 2017. The following table sets forth information on interest expense (in thousands):

	Year Ended December 31,	
	2018	**2017**
Convertible notes:		
Non-cash amortization of the debt discount and debt issuance costs	$ 35,173	$ 32,536
Interest expense payable in cash	6,855	7,090
Non-cash interest expense for long-term financing liability	—	3,352
Interest on mortgage for primary R&D and manufacturing facilities	2,409	1,103
Other	352	671
Total interest expense	$ 44,789	$ 44,752

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.

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.

Other Expenses

Other expenses were $0.2 million in 2018 and $3.5 million for 2017. Our 2017 other expenses 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

We had an income tax benefit of $291.1 million for 2018, compared to $6.0 million for 2017. Our tax benefit increased significantly in 2018 primarily due to a one-time, non-cash tax benefit related to the reversal of the valuation allowance previously recorded against Ionis' stand-alone U.S. federal net deferred tax assets of $332.1 million. Because of Ionis' strong financial performance, on a stand-alone basis, over the past few years and our outlook regarding the continued growth of our business, we determined that it is more likely than not that we will utilize most of our deferred federal income tax assets primarily net operating loss carryforwards and research and development and orphan drug credit carryforwards. We continue to maintain a valuation allowance against certain Ionis and Akcea federal and state net deferred tax assets at December 31, 2018 due to uncertainties related to our ability to realize the tax benefits associated with these assets.

Net Income (Loss)

We had income of $215.0 million for 2018, compared to a net loss of $10.8 million for 2017. The increase in our net income in 2018, compared to 2017 was primarily due to our increasing revenues and income tax benefit.

Net Operating Loss and Tax Credit Carryforwards

At December 31, 2018, we had federal and California tax net operating loss carryforwards of $284.6 million and $808.7 million, respectively. Our federal tax loss carryforwards begin to expire in 2033. A portion of our California tax loss carryforwards continued to expire in 2018. At December 31, 2018, we also had federal and California research and development tax credit carryforwards of $288.9 million and $68.4 million, respectively. Our Federal research and development tax credit carryforwards began 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.

At December 31, 2018, we owned approximately 75 percent of Akcea. The shares of Akcea third parties own represent an interest in Akcea's equity that we do not control. However, because we continue to maintain overall control of Akcea through our voting interest, we reflect the assets, liabilities and results of operations of Akcea in our consolidated financial statements. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line called “Net loss attributable to noncontrolling interest in Akcea” on our statement of operations. Our noncontrolling interest in Akcea on our statement of operations for 2018 was $58.8 million, compared to $11.1 million for 2017.

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

We had net income attributable to our common stockholders of $273.7 million for 2018, compared $0.3 million in 2017. Basic and diluted net income per share for 2018 was $2.09 and $2.07, respectively compared to $0.15 for 2017. The increase in our net income attributable to our common stockholders in 2018, compared to 2017, was primarily due to our increasing revenues and income tax benefit, slightly offset by an increase in the net loss related to the portion of Akcea we own.

Years Ended December 31, 2017 and December 31, 2016

Revenue

Total revenue for 2017 was $514.2 million compared to $372.8 million for 2016 and was comprised of the following (amounts in thousands):

	Year Ended December 31,	
	2017	**2016**
Revenue:		**(as revised)**
Commercial revenue:		
SPINRAZA royalties	$ 112,540	$ 883
Licensing and other royalty revenue	7,474	21,884
Total commercial revenue	120,014	22,767
R&D revenue:		
Amortization from upfront payments	97,646	62,415
Milestone payments	152,008	152,325
License fees	116,095	98,000
Other services	28,416	37,269
Total R&D revenue	394,165	350,009
Total revenue	$ 514,179	$ 372,776

The increase in revenue in 2017 compared to 2016 was primarily due to increasing commercial revenue from SPINRAZA royalties. SPINRAZA was approved by the FDA in December 2016, making 2017 the first full year we earned commercial revenue from SPINRAZA.

Our revenue from licensing and other royalties was higher in 2016 primarily from $15 million we earned from Kastle when it acquired the global rights to develop and commercialize Kynamro.

R&D revenue from the amortization of upfront payments increased $35 million in 2017, compared to 2016, primarily due to the amortization of the upfront payment from our collaboration with Novartis which began in the first quarter of 2017.

In 2017, R&D revenue from milestone payments included over $120 million of milestone payments from Biogen, including the milestone payments for SPINRAZA approval in the EU and Japan. In 2016, R&D revenue from milestone payments included over $115 million of milestone payments from Biogen, including a $60 million milestone payment for the approval of SPINRAZA in the U.S.

In 2017, we earned $65 million from Bayer for the license of IONIS-FXI-L_{Rx} and $45 million from Roche for the license of IONIS-HTT_{Rx}. In 2016 we earned $91.2 million when Bayer licensed IONIS-FXI_{Rx}.

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 prepared to commercialize TEGSEDI and WAYLIVRA. 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

Research, Development and Patent 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, total 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 other activities in support of TEGSEDI and WAYLIVRA. If you exclude these expenses, our research, development and patent expenses decreased year-over-year. 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

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
WAYLIVRA	22,524	26,285
TEGSEDI	24,880	22,939
Other antisense development products	79,106	42,999
Development overhead expenses	43,784	42,966
Total antisense drug development, excluding non-cash compensation expense related to equity awards	181,290	179,057
Non-cash compensation expense related to equity awards	28,325	21,380
Total antisense drug development expenses	$ 209,615	$ 200,437

Antisense drug development expenditures were $181.3 million for 2017 compared to $179.1 million for 2016. The expenses for SPINRAZA and WAYLIVRA declined in 2017. Specifically, we transitioned all further development of SPINRAZA to Biogen and we were completing our Phase 3 WAYLIVRA trial in patients with FCS. Additionally, we completed our Phase 3 TEGSEDI trial in patients with hATTR with polyneuropathy in 2017. Our 2017 expenses included $4.8 million of expenses related to regulatory filing activities for TEGSEDI and WAYLIVRA. 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	$ 123,934	$ 132,418
Akcea Therapeutics	105,751	46,639
Elimination of intercompany activity	(48,395)	—
Subtotal	181,290	179,057
Non-cash compensation expense related to equity awards	28,325	21,380
Total antisense drug development expenses	$ 209,615	$ 200,437

Manufacturing and Operations

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 for 2017 were $43.5 million and were higher compared to $30.1 million for 2016. All amounts exclude non-cash compensation expense related to equity awards. $11 million of the increase in manufacturing expenses was related to TEGSEDI and WAYLIVRA to prepare for the planned launches. 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

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 essentially 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

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 for 2017 were $87.0 million and increased compared to $31.6 million for 2016. The increase in SG&A expenses was principally due to the cost of preparing to commercialize TEGSEDI and WAYLIVRA and from fees we owed under our in-licensing agreements related to SPINRAZA. 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

Akcea's operating expenses 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 WAYLIVRA. 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 totaled $8.2 million compared to $5.5 million for 2016. Investment income increased primarily due to a higher average cash balance and an improvement in the market conditions during 2017 compared to 2016.

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.

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 Expense (Benefit)

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.

Net Loss

Net loss for 2017 was $10.8 million compared $60.4 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 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 $11.1 million. We also added a corresponding account to our consolidated balance sheet called "Noncontrolling interest in Akcea Therapeutics, Inc."

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

We had net income attributable to our common stockholders of $0.3 million for 2017, compared to a net loss of $60.4 million in 2016. Basic and diluted net income per share for 2017 was $0.15 compared to basic and dilutive net loss per share of $0.50 for 2016.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. Beginning in December 2016 we added commercial revenue from SPINRAZA royalties. From our inception through December 31, 2018, we had earned approximately $3.2 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, 2018, we had raised net proceeds of approximately $1.7 billion from the sale of our equity securities, not including the $182.4 million Akcea received in net proceeds from its IPO in July 2017. Additionally, we borrowed approximately $1.4 billion under long-term debt arrangements to finance a portion of our operations over the same time period.

At December 31, 2018, we had cash, cash equivalents and short-term investments of $2.1 billion and stockholders' equity of $1,187.2 million. In comparison, we had cash, cash equivalents and short-term investments of $1.0 billion and stockholders' equity of $365.3 million at December 31, 2017. Our cash, cash equivalents and short-term investments increased in 2018 primarily from the $1 billion payment we received from Biogen for our 2018 strategic neurology collaboration.

At December 31, 2018, we had consolidated working capital of $1.9 billion compared to $925.1 million at December 31, 2017. As of December 31, 2018, our debt and other obligations totaled $764.0 million compared to $759.8 million at December 31, 2017.

The following table summarizes our contractual obligations as of December 31, 2018. 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)	$ 706.1	$ 6.9	$ 699.2	$ —	$ —
Building mortgage payments	$ 80.7	$ 2.4	$ 4.8	$ 6.2	$ 67.3
Financing arrangements (principal and interest payable)	$ 12.7	$ 12.7	$ —	$ —	$ —
Other obligations (principal and interest payable)	$ 1.0	$ 0.1	$ 0.1	$ 0.1	$ 0.7
Operating leases	$ 25.7	$ 3.1	$ 5.7	$ 5.0	$ 11.9
Total	$ 826.2	$ 25.2	$ 709.8	$ 11.3	$ 79.9

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 $68.3 million of gross unrecognized tax benefits from our contractual obligations table above.

1 Percent Convertible Senior Notes

In November 2014, we completed a $500 million offering of convertible senior notes, which mature in 2021 and bear interest at 1 percent. We used a substantial portion of the net proceeds from the issuance of the 1 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, 2018, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At December 31, 2018, 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, 2018 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.

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 and the building that houses our manufacturing facility for $79.4 million and $14.0 million, respectively. 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, 2018 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, 2018.

Management's Report on Internal Control over Financial Reporting

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

As of December 31, 2018, 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, 2018.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2018, as stated in their attestation report, which is included elsewhere herein.

Changes in Internal Control over Financial Reporting

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

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

Opinion on Internal Control over Financial Reporting
We have audited Ionis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2018, 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, 2018, 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, 2018 and 2017, and the related consolidated statements of operations, comprehensive income (loss), stockholders' equity and cash flows for each of the three years in the period ended December 31, 2018, and the related notes and our report dated March 1, 2019 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
March 1, 2019

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, 2018 (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.

Section 16(a) Beneficial Ownership Reporting Compliance

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, 2018.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance	
Equity compensation plans approved by stockholders(a)	11,311,944	$ 47.85	4,578,854	(b)
Total	11,311,944	$ 47.85	4,578,854	

(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, 774,816 remained available for purchase under the ESPP as of December 31, 2018. The ESPP incorporates an evergreen formula pursuant to which on January 1 of each year on the first nine anniversaries of the plan, we automatically increase the aggregate number of shares reserved for issuance under the plan by 150,000 shares.

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

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

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

Item 14. Principal Accounting Fees and Services

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

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Index to Financial Statements

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

(a)(2) Index to Financial Statement Schedules

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

(a)(3) Index to Exhibits

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
3.2	Certificate of Amendment to Restated Certificate of Incorporation, filed June 17, 2014. - Filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement, for the 2014 Annual Meeting of Stockholders, filed with the SEC on April 25, 2014, and incorporated herein by reference.
3.3	Certificate of Amendment to Restated Certificate of Incorporation, filed December 18, 2015. - Filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 18, 2015 and incorporated herein by reference.
3.4	Amended and Restated Bylaws, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 18, 2015 and incorporated herein by reference.
4.1	Certificate of Designation of the Series C Junior Participating Preferred Stock, filed as an exhibit to Registrant's Report on Form 8-K dated filed December 13, 2000 and incorporated herein by reference.
4.2	Specimen Common Stock Certificate, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
4.3	Indenture, dated as of August 13, 2012, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 2¾ percent Convertible Senior Note due 2019, filed as an exhibit to the Registrant's Report on Form 8-K filed August 13, 2012 and incorporated herein by reference.
4.4	Indenture, dated as of November 17, 2014, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 1.00 percent Convertible Senior Note due 2021, filed as an exhibit to the Registrant's Current Report on Form 8-K filed November 21, 2014 and incorporated herein by reference.
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, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
10.5	Collaboration and License Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001, filed as an exhibit to the Registrant's report on Form 10-Q as amended for the quarter ended June 30, 2001 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.6	Amendment #1 to the Research, Development and License Agreement dated May 11, 2011 by and between the Registrant and Glaxo Group Limited, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2011 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.7	Amended and Restated Collaboration and License Agreement between the Registrant and Antisense Therapeutics Ltd dated February 8, 2008, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2008 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.8	Amended and Restated License Agreement between the Registrant and Atlantic Pharmaceuticals Limited dated November 30, 2009, 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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.9	Stock Purchase Agreement among the Registrant, Akcea Therapeutics, Inc. and Novartis Pharma AG dated January 5, 2017, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 and incorporated herein by reference.
10.10	Amendment #1 between the Registrant and Bayer AG dated February 10, 2017, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.11	Registrant's Amended and Restated 10b5-1 Trading Plan dated September 12, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013 and incorporated herein by reference.
10.12*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended, filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement, for the 2014 Annual Meeting of Stockholders, filed with the SEC on April 25, 2014, and incorporated herein by reference.
10.13*	Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012 and incorporated herein by reference.
10.14	Research Collaboration, Option and License Agreement between the Registrant and Biogen MA Inc. dated December 19, 2017, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.15*	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.
10.16*	Form of Option Agreement under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference.
10.17*	Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed with the SEC on August 8, 2011, and incorporated herein by reference.
10.18	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.
10.19*	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.
10.20*	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.
10.21	Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated March 30, 2010, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2010 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.22	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.
10.23	Research Agreement dated August 10, 2011 between the Registrant and CHDI Foundation, Inc, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2011 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.24	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.
10.25	Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated January 3, 2012, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.26	DMPK Research, Development, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated June 27, 2012, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.27	Amendment #2 to Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated October 30, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.28	Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated December 7, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.29	Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated December 10, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.30	HTT Research, Development, Option and License Agreement among the Registrant, F. Hoffmann-La Roche Ltd and Hoffman-La Roche Inc. dated April 8, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.31	Letter Agreement between the Registrant and CHDI Foundation, Inc. dated April 8, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.32	Amendment #1 to Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated August 13, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.33	Letter Agreement Amendment between the Registrant and Biogen Idec International Holding Ltd dated January 27, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.34	Amendment No. 3 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated July 10, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.35	Amendment #4 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated April 10, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.36	Amendment #5 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated June 27, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.37	Exclusive License Agreement between the Registrant and the University of Massachusetts dated January 14, 2010, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.38	Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated October 26, 2011, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.39	Amendment to Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated March 14, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.40	Amendment #1 to the Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated December 15, 2014, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.41	Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 22, 2014, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.42	Amendment No.2 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated October 15, 2014, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.43	Strategic Collaboration Agreement between the Registrant and AstraZeneca AB dated July 31, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.44	Amendment #6 to Research, Development and License Agreement between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated September 2, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.45	Amendment Number One to the Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated July 13, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.46	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.
10.47	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.
10.48	Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated January 8, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.49	Amendment #1 to HTT Research, Development, Option and License Agreement between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. dated January 9, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.50	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.
10.51	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.
10.52	Amendment No.3 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated January 18, 2016, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.53	Amendment #7 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated March 4, 2016, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.54	First Amendment to Research Collaboration, Option and License Agreement between the Registrant and Janssen Biotech Inc. dated December 21, 2016, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.55	Letter Agreement between the Registrant and Biogen MA Inc. dated October 28, 2016, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.56	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.
10.57	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.
10.58	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.
10.59*	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.
10.60*	Registrant's Severance Benefit Plan and Summary Plan Description dated October 18, 2018, - filed as an exhibit to the Registrant's Current Report on form 8-K filed October 18, 2018 and incorporated herein by reference.
10.61	Strategic Advisory Services Agreement by and between the Registrant and B. Lynne Parshall, dated January 15, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 and incorporated herein by reference.
10.62	Development, Commercialization, Collaboration, and License Agreement by and between the Registrant and Akcea Therapeutics, Inc., dated March 14, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 and incorporated herein by reference.
10.63	Amended and Restated Services Agreement by and between the Registrant and Akcea Therapeutics, Inc., dated March 14, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 and incorporated herein by reference.
10.64	New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated April 19, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.65	Stock Purchase Agreement by and between the Registrant and Biogen MA Inc., dated April 19, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2018 and incorporated herein by reference.
10.66	Second Amendment to Research, Collaboration, Option and License Agreement by and between the Registrant and Janssen Biotech Inc., dated August 7, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.67	Factor B Development Collaboration, Option and License Agreement by and between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., dated October 9, 2018. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.68	Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc, dated October 17, 2018. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.69	Amendment #1 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.70	Amendment #4 to the Collaboration, License and Development Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
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, 2018, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of comprehensive income (loss), (iv) consolidated statements of stockholders' equity, (v) consolidated statements of cash flows, and (vi) notes to consolidated financial statements (detail tagged).

* 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 1st day of March, 2019.

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)	March 1, 2019
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Senior Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	March 1, 2019
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director and Senior Strategic Advisor	March 1, 2019
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	March 1, 2019
/s/ BREAUX CASTLEMAN Breaux Castleman	Director	March 1, 2019
/s/ MICHAEL HAYDEN Michael Hayden, CM OBC MB ChB PhD FRCP(C) FRSC	Director	March 1, 2019
/s/ JOSEPH KLEIN Joseph Klein, III	Director	March 1, 2019
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Director	March 1, 2019
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	March 1, 2019
/s/ PETER N. REIKES Peter N. Reikes	Director	March 1, 2019
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	March 1, 2019

IONIS PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

Opinion on the Financial Statements
We have audited the accompanying consolidated balance sheets of Ionis Pharmaceuticals, Inc. (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations, comprehensive income (loss), stockholders' equity and cash flows for each of the three years in the period ended December 31, 2018, 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, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, 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, 2018, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 Framework), and our report dated March 1, 2019 expressed an unqualified opinion thereon.

Adoption of ASU No. 2014-09, Revenue Recognition
As discussed in Note 1 to the consolidated financial statements, the Company changed its method of accounting for revenue for all years presented, 2016 through 2018, due to the adoption of ASU No. 2014-09, Revenue from Contracts with Customers (Topic 606).

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures 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
March 1, 2019

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

	December 31,	
	2018	**2017**
ASSETS		**(as revised*)**
Current assets:		
Cash and cash equivalents	$ 278,820	$ 129,630
Short-term investments	1,805,252	893,085
Contracts receivable	12,759	62,955
Inventories	8,582	9,982
Other current assets	102,473	73,082
Total current assets	2,207,886	1,168,734
Property, plant and equipment, net	132,160	121,907
Patents, net	24,032	22,004
Long-term deferred tax assets	290,796	—
Deposits and other assets	12,910	10,129
Total assets	$ 2,667,784	$ 1,322,774
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 28,660	$ 24,886
Accrued compensation	29,268	25,151
Accrued liabilities	48,361	66,618
Current portion of long-term obligations	13,749	1,621
Current portion of deferred contract revenue	160,256	125,336
Total current liabilities	280,294	243,612
Long-term deferred contract revenue	567,359	108,026
1 percent convertible senior notes	568,215	533,111
Long-term obligations, less current portion	4,914	12,974
Long-term mortgage debt	59,842	59,771
Total liabilities	1,480,624	957,494
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 137,928,828 and 124,976,373 shares issued and outstanding at December 31, 2018 and December 31, 2017, respectively	138	125
Additional paid-in capital	2,047,250	1,553,681
Accumulated other comprehensive loss	(32,016)	(31,759)
Accumulated deficit	(967,293)	(1,241,034)
Total Ionis stockholders' equity	1,048,079	281,013
Noncontrolling interest in Akcea Therapeutics, Inc.	139,081	84,267
Total stockholders' equity	1,187,160	365,280
Total liabilities and stockholders' equity	$ 2,667,784	$ 1,322,774

* Our 2017 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. Refer to Note 1, *Organization and Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Years Ended December 31,		
	2018	2017	2016
		(as revised*)	
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 237,930	$ 112,540	$ 883
TEGSEDI product sales, net	2,237	—	—
Licensing and other royalty revenue	14,755	7,474	21,884
Total commercial revenue	254,922	120,014	22,767
Research and development revenue under collaborative agreements	344,752	394,165	350,009
Total revenue	599,674	514,179	372,776
Expenses:			
Cost of products sold	1,820	—	—
Research, development and patent	414,604	374,644	344,320
Selling, general and administrative	244,622	108,488	48,616
Total operating expenses	661,046	483,132	392,936
Income (loss) from operations	(61,372)	31,047	(20,160)
Other income (expense):			
Investment income	30,187	8,179	5,472
Interest expense	(44,789)	(44,752)	(38,795)
Loss on extinguishment of financing liability for leased facility	—	(7,689)	—
Loss on early retirement of debt	—	—	(3,983)
Other expenses	(182)	(3,548)	—
Loss before income tax benefit (expense)	(76,156)	(16,763)	(57,466)
Income tax benefit (expense)	291,141	5,980	(2,934)
Net income (loss)	214,985	(10,783)	(60,400)
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	58,756	11,129	—
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 273,741	$ 346	$ (60,400)
Basic net income (loss) per share	$ 2.09	$ 0.15	$ (0.50)
Shares used in computing basic net income (loss) per share	132,320	124,016	120,933
Diluted net income (loss) per share	$ 2.07	$ 0.15	$ (0.50)
Shares used in computing diluted net income (loss) per share	134,056	126,098	120,933

* Our 2017 and 2016 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. Refer to Note 1, *Organization and Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Years Ended December 31,		
	2018	2017	2016
		(as revised*)	
Net income (loss)	$ 214,985	$ (10,783)	$ (60,400)
Unrealized losses on investments, net of tax	(280)	(960)	(17,219)
Reclassification adjustment for realized (gains) losses included in net loss	—	(374)	447
Currency translation adjustment	23	(67)	(21)
Comprehensive income (loss)	214,728	(12,184)	(77,193)
Comprehensive loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	(58,781)	(11,224)	—
Comprehensive income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 273,509	$ (960)	$ (77,193)

* Our 2017 and 2016 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. Refer to Note 1, *Organization and Significant Accounting Policies*, for further information.

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
Years Ended December 31, 2018, 2017 (*as revised) and 2016 (*as revised)
(In thousands)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at December 31, 2015	120,351	$ 120	$ 1,309,107	$ (13,565)	$ (1,094,872)	$ 200,790	$ —	$ 200,790
Cumulative adjustment related to adopting Topic 606 revenue recognition guidance	—	—	—	—	(86,108)	(86,108)	—	(86,108)
Net loss	—	—	—	—	(60,400)	(60,400)	—	(60,400)
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)	$ (1,241,380)	$ 39,613	$ —	$ 39,613
Net income	—	—	—	—	346	346	—	346
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.	—	—	(5,110)	—	—	(5,110)	(6,114)	(11,224)
Balance at December 31, 2017	124,976	$ 125	$ 1,553,681	$ (31,759)	$ (1,241,034)	$ 281,013	$ 84,267	$ 365,280
Net income	—	—	—	—	273,741	273,741	—	273,741
Change in unrealized gains (losses), net of tax	—	—	—	(280)	—	(280)	—	(280)
Foreign currency translation	—	—	—	23	—	23	—	23

Biogen stock purchase	11,502	11	447,954	—	—	447,965	—	447,965
Issuance of common stock in connection with employee stock plans	1,451	2	27,898	—	—	27,900	—	27,900
Share-based compensation expense	—	—	131,312	—	—	131,312	—	131,312
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(113,595)	—	—	(113,595)	54,814	(58,781)
Balance at December 31, 2018	137,929	$ 138	$ 2,047,250	$ (32,016)	$ (967,293)	$ 1,048,079	$ 139,081	$ 1,187,160

* Our 2017 and 2016 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. Refer to Note 1, *Organization and Significant Accounting Policies*, for further information.

See accompanying notes.

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

	Years Ended December 31,		
	2018	2017	2016
		(as revised*)	
Operating activities:			
Net income (loss)	$ 214,985	$ (10,783)	$ (60,400)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Depreciation	10,706	6,708	7,481
Amortization of patents	1,822	1,641	1,552
Amortization of premium (discount) on investments, net	(1,013)	6,752	6,813
Amortization of debt issuance costs	1,810	1,616	1,225
Amortization of convertible senior notes discount	33,363	30,920	23,890
Amortization of long-term financing liability for leased facility	—	3,659	6,693
Stock-based compensation expense	131,312	85,975	72,108
Gain on investment in Regulus Therapeutics Inc.	—	(374)	—
Loss on extinguishment of financing liability for leased facility	—	7,689	—
Loss on early retirement of debt	—	—	3,983
Deferred income taxes (including benefit from valuation allowance release)	(290,516)	—	—
Non-cash losses related to patents, licensing, property, plant and equipment and strategic investments	1,012	3,302	2,297
Changes in operating assets and liabilities:			
Contracts receivable	47,595	45,088	(96,687)
Inventories	1,400	(2,493)	(590)
Other current and long-term assets	(29,348)	(58,367)	1,603
Long-term income tax receivable	(223)	(9,114)	—
Accounts payable	(655)	1,784	(10,677)
Income taxes	(710)	435	1,069
Accrued compensation	4,117	965	8,121
Accrued liabilities and deferred rent	(17,023)	28,564	4,720
Deferred contract revenue	494,254	30,182	(85,306)
Net cash provided by (used in) operating activities	602,888	174,149	(112,105)
Investing activities:			
Purchases of short-term investments	(1,794,735)	(877,810)	(300,912)
Proceeds from the sale of short-term investments	882,824	557,369	364,572
Purchases of property, plant and equipment	(13,608)	(34,764)	(7,107)
Acquisition of licenses and other assets, net	(4,044)	(3,093)	(4,421)
Purchase of strategic investments	—	(2,500)	—
Proceeds from the sale of Regulus Therapeutics, Inc.	—	2,507	4,467
Net cash (used in) provided by investing activities	(929,563)	(358,291)	56,599
Financing activities:			
Proceeds from equity, net	27,900	22,931	13,417
Proceeds from issuance of common stock in Akcea Therapeutics, Inc. from its initial public offering, net of underwriters' discount	—	110,438	—
Proceeds from building mortgage debt, net of issuance costs	—	59,750	—
Proceeds from the issuance of common stock to Biogen	447,965	—	—
Proceeds from the issuance of common stock to Novartis	—	71,737	—
Proceeds from borrowing on line of credit facility	—	—	4,000
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
Principal payments on debt and capital lease obligations	—	(3,599)	(7,066)
Net cash provided by financing activities	475,865	229,087	11,394
Net increase (decrease) in cash and cash equivalents	149,190	44,945	(44,112)
Cash and cash equivalents at beginning of year	129,630	84,685	128,797
Cash and cash equivalents at end of year	$ 278,820	$ 129,630	$ 84,685

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

	Years Ended December 31,		
	2018	2017	2016
		(as revised*)	
Supplemental disclosures of cash flow information:			
Interest paid	$ 9,592	$ 8,035	$ 7,313
Supplemental disclosures of non-cash investing and financing activities:			
Amounts accrued for capital and patent expenditures	$ 4,428	$ 1,983	$ 3,439
Purchases of property, plant and equipment included in long-term obligations	$ 3,350	$ —	$ —
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

* Our 2017 and 2016 amounts are revised to reflect the new revenue recognition accounting guidance, which we adopted retrospectively in the first quarter of 2018. Refer to Note 1, *Organization and Significant Accounting Policies*, for further information.

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. From the closing of Akcea's IPO in July 2017 through mid-April 2018, we owned approximately 68 percent of Akcea. In the second, third and fourth quarters of 2018, we received additional shares of Akcea's stock related to our license of TEGSEDI and AKCEA-TTR-L_{Rx} to Akcea, increasing our ownership percentage to approximately 75 percent. We reflected the increase in our ownership in these financial statements. In the first quarter of 2019, Akcea will pay us a $75 million sublicense fee in Akcea common stock, as a result of Novartis' license of AKCEA-APO(a)-L_{Rx} in February 2019. We will receive 2.8 million shares of Akcea common stock for the sublicense fee. 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 medicines using antisense technology. In December 2015, we changed our name from Isis Pharmaceuticals, Inc. to Ionis Pharmaceuticals, Inc.

Basic and Diluted Net Income (Loss) per Share

Basic net income (loss) per share

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

The calculation of total net income (loss) attributable to our common stockholders for 2018 and 2017 considered our net income for Ionis on a stand-alone basis plus our share of Akcea's net loss for the period. During 2016, we owned 100 percent of Akcea. To calculate the portion of Akcea's net loss attributable to our ownership for 2018 and 2017, we multiplied Akcea's loss per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net income (loss) available to Ionis common stockholders for the calculation of net income (loss) per share is different than net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders in our consolidated statements of operations for 2018 and 2017.

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

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

Prior to Akcea's IPO in July 2017, we owned Akcea series A convertible preferred stock, which included a six percent cumulative dividend. Upon completion of Akcea's IPO in July 2017, our preferred stock was converted into common stock on a 1:1 basis. The preferred stock dividend was not paid at the IPO because the IPO was not a liquidation event or a change in control. During 2017, Akcea used a two-class method to compute its net 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 that we owned in our calculation of basic and diluted net income (loss) per share for year ended December 31, 2017.

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

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

Dilutive net income (loss per share)

For 2018 and 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.

We calculated our diluted net income per share for 2018 as follows (in thousands except per share amounts):

Year Ended December 31, 2018	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 276,868	132,320	$ 2.09
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,216	
Shares issuable upon restricted stock award issuance	—	514	
Shares issuable related to our ESPP	—	6	
Income available to Ionis common stockholders, plus assumed conversions	$ 276,868	134,056	$ 2.07

We calculated our diluted net income per share for 2017 as follows (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	$ 18,792	124,016	$ 0.15
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	1,619	
Shares issuable upon restricted stock award issuance	—	459	
Shares issuable related to our ESPP	—	4	
Income available to Ionis common stockholders, plus assumed conversions	$ 18,792	126,098	$ 0.15

For 2018 and 2017, the calculation excluded our convertible notes because the effect on diluted earnings per share was anti-dilutive.

For 2016, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 1 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

Adoption of New Revenue Recognition Accounting Standard (Topic 606)

In May 2014, the FASB issued accounting guidance on the recognition of revenue from customers. This guidance supersedes the revenue recognition requirements we previously followed in Accounting Standards Codification, or ASC, Topic 605, *Revenue Recognition*, or Topic 605, and created a new Topic 606, *Revenue from Contracts with Customers*, or Topic 606. Under Topic 606, 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. We adopted Topic 606 on January 1, 2018 under the full retrospective approach, which required us to revise our prior period revenue. Under Topic 606, we were required to review all of our ongoing collaboration agreements in which we recognized revenue after January 1, 2016. We were required to assess what our revenue would have been for the period from January 1, 2016 to December 31, 2017 under Topic 606. As a result of this analysis, we determined that the cumulative revenue we would have recognized under Topic 606 decreased by $86.1 million. We recorded this amount as a cumulative adjustment to our accumulated deficit as of January 1, 2016 on our revised statement of stockholders' equity. We have labeled our prior period financial statements "as revised" to indicate the change required under the accounting rules.

The following tables summarize the adjustments we were required to make to amounts we originally reported in 2017 and 2016 to adopt Topic 606 (in thousands, except per share amounts):

Consolidated Balance Sheet

	At December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Current portion of deferred contract revenue	$ 106,465	$ 18,871	$ 125,336
Long-term portion of deferred contract revenue	$ 72,708	$ 35,318	$ 108,026
Accumulated deficit	$ (1,187,398)	$ (53,636)	$ (1,241,034)
Noncontrolling interest in Akcea Therapeutics, Inc.	$ 87,847	$ (3,580)	$ 84,267
Total stockholders' equity	$ 418,719	$ (53,439)	$ 365,280

Consolidated Statements of Operations

	Year Ended December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 112,540	$ -	$ 112,540
Licensing and other royalty revenue	9,519	(2,045)	7,474
Total commercial revenue	122,059	(2,045)	120,014
Research and development revenue under collaborative agreements	385,607	8,558	394,165
Total revenue	$ 507,666	$ 6,513	$ 514,179
Income from operations	$ 24,534	$ 6,513	$ 31,047
Net income (loss)	$ (17,296)	$ 6,513	$ (10,783)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (5,970)	$ 6,316	$ 346
Net income per share, basic and diluted	$ 0.08	$ 0.07	$ 0.15

	Year Ended December 31, 2016		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 883	$ —	$ 883
Licensing and other royalty revenue	19,839	2,045	21,884
Total commercial revenue	20,722	2,045	22,767
Research and development revenue under collaborative agreements	325,898	24,111	350,009
Total revenue	$ 346,620	$ 26,156	$ 372,776
Income (loss) from operations	$ (46,316)	$ 26,156	$ (20,160)
Net income (loss)	$ (86,556)	$ 26,156	$ (60,400)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (86,556)	$ 26,156	$ (60,400)
Net income (loss) per share, basic and diluted	$ (0.72)	$ 0.22	$ (0.50)

Consolidated Statements of Cash Flows

	Year Ended December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Net income (loss)	$ (17,296)	$ 6,513	$ (10,783)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Deferred contract revenue	$ 36,695	$ (6,513)	$ 30,182
Cash and cash equivalents at beginning of year	$ 84,685	$ —	$ 84,685
Cash and cash equivalents at end of year	$ 129,630	$ —	$ 129,630

	Year Ended December 31, 2016		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Net income (loss)	$ (86,556)	$ 26,156	$ (60,400)
Adjustments to reconcile net income (loss) to net cash provided by (used in) operating activities:			
Deferred contract revenue	$ (59,150)	$ (26,156)	$ (85,306)
Cash and cash equivalents at beginning of year	$ 128,797	$ —	$ 128,797
Cash and cash equivalents at end of year	$ 84,685	$ —	$ 84,685

Under Topic 606, compared to Topic 605, our total revenue increased $6.5 million for 2017 and $26.2 million for 2016. The change in our revenue was primarily due to:

- A change in how we recognize milestone payments: Topic 606 requires us to amortize more of the milestone payments we achieve, rather than recognizing the milestone payments in full in the period in which we achieved the milestone event as we did under Topic 605. This change resulted in an increase in R&D revenue recognized for 2017 and 2016 of $23.7 million and $24.1 million, respectively.

- A change in how we calculate revenue for payments we are recognizing into revenue over time: Under Topic 605, we amortized payments into revenue evenly over the period of our obligations. When we made a change to our estimated completion period, we recognized that change on a prospective basis. Under Topic 606, we are required to use an input method to determine the amount we amortize each reporting period. Each period we review our "inputs" such as our level of effort expended, including the time we estimate it will take us to complete the activities or costs incurred, relative to the total expected inputs to satisfy the performance obligation. For certain collaborations, such as Bayer and Novartis, the input method resulted in a change to the revenue we had previously recognized using a straight-line amortization method. This change resulted in a decrease in our R&D revenue of $15.1 million for 2017. This change did not result in an impact to our 2016 R&D revenue.

Our updated revenue recognition policy reflecting Topic 606 is as follows:

Our Revenue Sources

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

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

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

Commercial Revenue: TEGSEDI Product Sales, net

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

Research and development revenue under collaborative agreements

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

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

Steps to Recognize Revenue

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

1. Identify the contract

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

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

2. Identify the performance obligations

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

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

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

3. Determine the transaction price

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

Milestone payments are our most common type of variable consideration. We recognize milestone payments using the most likely amount method because we will either receive the milestone payment or we will not, which makes the potential milestone payment a binary event. The most likely amount method requires us to determine the likelihood of earning the milestone payment. We include a milestone payment in the transaction price once it is probable we will achieve the milestone event. Most often, we do not consider our milestone payments probable until we or our partner achieve the milestone event because the majority of our milestone payments are contingent upon events that are not within our control and are usually based on scientific progress. For example, in the first quarter of 2019, we earned a $35 million milestone payment from Roche when it dosed the first patient in the Phase 3 study of IONIS-HTT_{Rx}. At December 31, 2018, we determined it was not probable that we could earn this milestone payment. As such, we did not recognize any revenue associated with it in 2018.

4. Allocate the transaction price

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

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

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

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

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

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

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

5. Recognize revenue

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

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

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

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We recognize royalty revenue in the period in which the counterparty sells the related product, which in certain cases may require us to estimate our royalty revenue. We recognize royalties from SPINRAZA sales in the period Biogen records the sale of SPINRAZA. Our accounting for SPINRAZA royalties did not change as a result of adopting Topic 606.

Commercial Revenue: TEGSEDI Product Sales, net

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

Reserves for TEGSEDI Product Sales

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

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

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

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

Trade discounts and allowances: We provide customary invoice discounts on TEGSEDI product sales to our U.S. customer for prompt payment. We record this discount as a reduction of TEGSEDI product sales in the period in which we recognize the related product revenue. In addition, we receive and pay for various distribution services from our U.S. customer and wholesalers in our U.S. distribution channel. For services we receive that are either not distinct from the sale of TEGSEDI or for which we cannot reasonably estimate the fair value, we classify such fees as a reduction of TEGSEDI product sales.

Product Returns: Our U.S. customer has return rights and the wholesalers have limited return rights primarily related to the expiration date of the TEGSEDI product. We estimate the amount of TEGSEDI product sales that our customer may return. We record our return estimate as an accrued refund liability on our consolidated balance sheet with a corresponding offset reducing our TEGSEDI product sales, in the same period we recognize the related sale. Based on our distribution model for TEGSEDI, contractual inventory limits with our customer and wholesalers and the price of TEGSEDI, we believe we will have minimal returns. Our customer in Germany only takes title to the product once it receives an order from a hospital or pharmacy and therefore does not maintain any inventory of TEGSEDI, as such we do not estimate returns in Germany.

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

Research and development revenue under collaboration agreements:

Upfront Payments

When we enter into a collaboration agreement with an upfront payment, we typically record the entire upfront payment as deferred revenue if our only performance obligation is for R&D services we will provide in the future. We amortize the upfront payment into revenue as we perform the R&D services. For example, under our new collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases, we received a $75 million upfront payment in the fourth quarter of 2018. We allocated the upfront payment to our single performance obligation, R&D services. We are amortizing the $75 million upfront payment using an input method over the estimated period of time we are providing R&D services. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion. Under Topic 605, we amortized upfront payments evenly over the period of our obligation.

Milestone Payments

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

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, in the third quarter of 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. Under Topic 606, we added this payment to the transaction price and allocated it to our R&D services performance obligation. We are recognizing revenue from this milestone payment over our estimated period of performance. Under Topic 605, this milestone payment was recognized in full in the third quarter of 2017, which was the period in which we achieved the milestone event.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event. For example, in the third quarter of 2018, we recognized a $10 million milestone payment when AstraZeneca initiated a Phase 1 study of IONIS-AZ4-2.5-L_{Rx}. We concluded that the milestone payment was not related to our R&D services performance obligation. Therefore, we recognized this milestone payment in full in the third quarter of 2018 because we do not have any performance obligations related to this milestone payment. Our revenue recognition of milestone payments we earn based on our partners' activities did not change as a result of adopting Topic 606.

License Fees

We generally recognize as revenue the total amount we determine to be the stand-alone selling price of a license when we deliver the license to our partner. This is because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery. For example, in the fourth quarter of 2018, we earned a $35 million license fee when Biogen licensed IONIS-$SOD1_{Rx}$ from us. Our recognition of license fees did not change as a result of adopting Topic 606.

Amendments to Agreements

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

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

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

For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. As part of the agreement, Bayer paid us a $100 million upfront payment. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis and for providing an initial supply of API. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. As part of the 2017 amendment, Bayer paid us $75 million. We are also eligible to receive milestone payments and tiered royalties on gross margins of IONIS-FXI$_{Rx}$ and IONIS-FXI-L$_{Rx}$. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of IONIS-FXI-L$_{Rx}$, to provide R&D services and to deliver API. We allocated the $75 million transaction price to these performance obligations. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements*, for further discussion of our accounting treatment for our Bayer collaboration. Our allocation of the consideration we received for the Bayer amendment did not change as a result of adopting Topic 606. However, the method in which we are recognizing revenue related to our R&D services performance obligation did change. We are amortizing revenue related to our R&D services performance obligation using the input method under Topic 606.

Multiple Agreements

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

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

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

For example, in the second quarter of 2018, we entered into two separate agreements with Biogen at the same time: a new strategic neurology collaboration agreement and a stock purchase agreement, or SPA. We evaluated the Biogen agreements to determine whether we should treat the agreements separately or combine them. We considered that the agreements were negotiated concurrently and in contemplation of one another. Based on these facts and circumstances, we concluded that we should evaluate the provisions of the agreements on a combined basis. Refer to Note 6, *Collaborative Arrangements and Licensing Agreements* for further discussion of the accounting treatment for the 2018 strategic neurology collaboration with Biogen.

Contracts Receivable

Our contracts receivable balance represents the amounts we have billed our partners for goods we have delivered or services we have performed that are due to us unconditionally. When we bill our partners with payment terms based on the passage of time, we consider the contract receivable to be unconditional. We typically receive payment within one quarter of billing our partner. Our contracts receivable balance as of December 31, 2017 did not change when we adopted Topic 606.

Unbilled SPINRAZA Royalties

Our unbilled SPINRAZA royalties represent our right to receive consideration from Biogen in advance of when we are eligible to bill Biogen for SPINRAZA royalties. We include these unbilled amounts in other current assets on our consolidated balance sheet. Our unbilled SPINRAZA royalties as of December 31, 2017 did not change when we adopted Topic 606.

Deferred Revenue

We are often entitled to bill our customers and receive payment from our customers in advance of our obligation to provide services or transfer goods to our partners. In these instances, we include the amounts in deferred revenue on our consolidated balance sheet. During the years ended December 31, 2018 and 2017, we recognized $105.3 million and $95.1 million of revenue from amounts that were in our beginning deferred revenue balances for those periods, respectively. Refer to our revenue recognition policy above detailing how we recognize revenue for further discussion.

The following table summarizes the adjustments we were required to make to our deferred revenue amounts to adopt Topic 606 (in thousands):

	At December 31, 2017		
	As Previously Reported under Topic 605	Topic 606 Adjustment	As Revised
Current portion of deferred contract revenue	$ 106,465	$ 18,871	$ 125,336
Long-term portion of deferred contract revenue	72,708	35,318	108,026
Total deferred revenue	$ 179,173	$ 54,189	$ 233,362

Our deferred revenue balance increased $54.2 million at December 31, 2017 under Topic 606, compared to Topic 605. The increase was primarily related to the change in the accounting for certain milestone payments and the way in which we amortize payments. Under Topic 605, we previously recognized the majority of the milestone payments we earned in the period we achieved the milestone event, which did not impact our deferred revenue balance. Under Topic 606 we are now amortizing more milestone payments over the period of our performance obligation, which adds to our deferred revenue balance. Additionally, under Topic 605 we amortized payments evenly over the period of our obligation. Under Topic 606, we are required to use an input method to determine the amount we amortize each reporting period. The increase in deferred revenue relates to agreements with the following partners:

- $24.2 million from Biogen;
- $15.9 million from AstraZeneca;
- $11.8 million from Novartis; and
- $ 2.3 million from other partners.

Cost of Products Sold

We obtained the first regulatory approval for TEGSEDI in July 2018, as a result we began recognizing cost of products sold expenses related to TEGSEDI. Our cost of products sold includes manufacturing costs, transportation and freight costs and indirect overhead costs associated with the manufacturing and distribution of TEGSEDI. We also may include certain period costs related to manufacturing services and inventory adjustments in cost of products sold. Prior to obtaining regulatory approval, we expensed a significant portion of the costs we incurred to produce the TEGSEDI supply we are using in the commercial launch as research and development expense. We previously recognized $0.1 million of costs to produce TEGSEDI related to the TEGSEDI commercial revenue we recognized in 2018.

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, 2018, 2017 and 2016, research and development expenses were $411.9 million, $372.5 million and $340.4 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, 2018, 2017 and 2016, research and development costs of approximately $58.7 million, $59.5 million and $187.1 million, respectively, were related to our partner agreements.

We capitalize costs consisting principally of outside legal costs and filing fees related to obtaining patents. We amortize patent costs over the useful life of the patent, beginning with the date the U.S. Patent and Trademark Office, or foreign equivalent, issues the patent. The weighted average remaining amortizable life of our issued patents was 10.1 years at December 31, 2018.

The cost of our patents capitalized on our consolidated balance sheet at December 31, 2018 and 2017 was $32.7 million and $30.8 million, respectively. Accumulated amortization related to patents was $8.7 million and $8.8 million at December 31, 2018 and 2017, 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)
2019	$ 1.7
2020	$ 1.6
2021	$ 1.5
2022	$ 1.4
2023	$ 1.3

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 2018, 2017 and 2016, patent expenses were $2.6 million, $2.1 million and $3.9 million, respectively, and included non-cash charges related to the write-down of our patent costs to their estimated net realizable values of $0.8 million, $0.4 million and $2.3 million, respectively.

Accrued Liabilities

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

	December 31,	
	2018	2017
Clinical expenses	$ 22,125	$ 16,347
In-licensing expenses	12,298	33,790
Other miscellaneous expenses	13,938	16,481
Total accrued liabilities	$ 48,361	$ 66,618

Noncontrolling Interest in Akcea Therapeutics, Inc.

Prior to Akcea's IPO in July 2017, we owned 100 percent of Akcea. From the closing of Akcea's IPO in July 2017 through mid-April 2018, we owned approximately 68 percent of Akcea. In the second, third and fourth quarters of 2018, we received additional shares of Akcea's stock related to our license of TEGSEDI and AKCEA-TTR-L_{Rx} to Akcea, increasing our ownership percentage to approximately 75 percent. We reflected this increase in our ownership percentage in these financial statements as an adjustment to noncontrolling interest. 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. We reflect the noncontrolling interest attributable to other owners of Akcea's common stock in a separate line on the statement of operations and a separate line within stockholders' equity in our consolidated balance sheet. In addition, we record a noncontrolling interest adjustment to account for the stock options Akcea grants, which if exercised, will dilute our ownership in Akcea. This adjustment is a reclassification within stockholders' equity from additional paid-in capital to noncontrolling interest in Akcea equal to the amount of stock-based compensation expense Akcea had recognized.

Concentration of Credit Risk

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

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

We also have equity investments of less than 20 percent ownership in publicly and privately held biotechnology companies that we received as part of a technology license or partner agreement. At December 31, 2018, we held equity investments in two publicly held companies, ProQR Therapeutics N.V., or ProQR, and Antisense Therapeutics Limited, or ATL. We also held equity investments in four privately-held companies, Atlantic Pharmaceuticals Limited, Dynacure SAS, Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd.

In January 2018, we adopted the amended accounting guidance related to the recognition, measurement, presentation, and disclosure of certain financial instruments. The amended guidance requires us to measure and record our equity investments at fair value. Additionally, the amended accounting guidance requires us to recognize the changes in fair value in our consolidated statement of operations, instead of through accumulated other comprehensive income. Prior to 2018, we accounted for our equity investments in privately held companies under the cost method of accounting. Under the amended guidance we account for our equity investments in privately held companies at their cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer. Our adoption of this guidance did not have an impact on our results.

Inventory Valuation

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

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

We review our inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value based on forecasted demand compared to quantities on hand. We consider several factors in estimating the net realizable value, including shelf life of our inventory, alternative uses for our medicines in development and historical write-offs. We did not record any inventory write-offs for the years ended December 31, 2018, 2017 or 2016. Total inventory was $8.6 million and $10.0 million as of December 31, 2018 and 2017, 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, 2018	December 31, 2017
Computer software, laboratory, manufacturing and other equipment	3 to 10	$ 53,496	$ 66,558
Building, building improvements and building systems	15 to 40	97,528	92,770
Land improvements	20	2,853	2,853
Leasehold improvements	5 to 15	18,981	26,748
Furniture and fixtures	5 to 10	6,283	6,161
		179,141	195,090
Less accumulated depreciation		(61,474)	(87,676)
		117,667	107,414
Land		14,493	14,493
Total		$ 132,160	$ 121,907

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

Fair Value of Financial Instruments

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

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, $0.8 million and $2.3 million for the years ended December 31, 2018, 2017 and 2016, respectively, related primarily to the write-down of intangible assets.

Use of Estimates

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

Stock-Based Compensation Expense

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

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

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

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

Accumulated Other Comprehensive Loss

Accumulated other comprehensive loss is primarily comprised of unrealized gains and losses on investments, net of taxes and adjustments we made to reclassify realized gains and losses on investments from other accumulated comprehensive loss to our Consolidated Statement of Operations. The following table summarizes changes in accumulated other comprehensive loss for the years ended December 31, 2018, 2017 and 2016 (in thousands):

	Year Ended December 31,		
	2018	2017	2016
Beginning balance accumulated other comprehensive loss	$ (31,759)	$ (30,358)	$ (13,565)
Unrealized losses on securities, net of tax (1)	(280)	(960)	(17,219)
Amounts reclassified from accumulated other comprehensive loss	—	(374)	447
Currency translation adjustment	23	(67)	(21)
Net other comprehensive loss for the period	(257)	(1,401)	(16,793)
Ending balance accumulated other comprehensive loss	$ (32,016)	$ (31,759)	$ (30,358)

(1) A tax benefit of $0.3 million was included in other comprehensive loss for the year ended December 31, 2018. There was no tax benefit or expense for other comprehensive loss for the years ended December 31, 2017 or 2016.

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. We use accounting estimates and assumptions when we determine the fair value of the debt component. These estimates and assumptions we use 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, our majority-owned affiliate. Akcea is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with rare and serious diseases. We provide segment financial information and results for our Ionis Core segment and our Akcea Therapeutics segment based on the segregation of revenues and expenses that our chief decision maker reviews to assess operating performance and to make operating decisions. We allocate a portion of Ionis' development, R&D support and general and administrative expenses to Akcea for work Ionis performs on behalf of Akcea.

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 2018 and 2017, 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.

The following tables present the major security types we held at December 31, 2018 and 2017 that are regularly measured and carried at fair value. At December 31, 2018, our ProQR investment was subject to trading restrictions through the fourth quarter of 2019, as a result we included a lack of marketability discount in valuing this investment, which is a Level 3 input. At December 31, 2017, we did not have any financial instruments that we valued using Level 3 inputs. 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, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 146,281	$ 146,281	$ —	$ —
Corporate debt securities (2)	1,252,960	—	1,252,960	—
Debt securities issued by U.S. government agencies (3)	276,612	—	276,612	—
Debt securities issued by the U.S. Treasury (4)	260,154	260,154	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	79,942	—	79,942	—
Investment in ProQR Therapeutics N.V. (5)	1,349	—	—	1,349
Total	$ 2,017,298	$ 406,435	$ 1,609,514	$ 1,349

	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 (6)	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 (7)	93,932	—	93,932
Total	$ 994,798	$ 117,080	$ 877,718

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

(2) $50.2 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(3) Included in short-term investments on our consolidated balance sheet.

(4) $14.2 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

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

(6) $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.

(7) $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.

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

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

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

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

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

For U.S. federal income tax purposes, we are required to file separate U.S. federal income tax returns for Ionis and Akcea. We began deconsolidating Akcea for U.S. federal income tax purposes upon Akcea's initial public offering. As a result, we are required to assess our Ionis stand-alone and Akcea's valuation allowances separately even though we consolidate Akcea's financial results in our consolidated financial statements. We continue to file combined state tax returns in most jurisdictions. As a result, we continue to assess the state portion of our valuation allowance for those jurisdictions on a consolidated basis.

We have historically recorded a valuation allowance against all our net deferred tax assets due to cumulative financial statement losses. However, in the fourth quarter of 2018, we reversed the valuation allowance previously recorded against our Ionis stand-alone U.S. federal net deferred tax assets, resulting in a one-time non-cash tax benefit of $332.1 million. Given our current stand-alone Ionis pre-tax income, and assuming we maintain this current level of Ionis stand-alone pre-tax income, we expect to generate income before taxes in the U.S. in future periods at a level that would result in us fully utilizing our U.S. federal net operating loss carryforwards and most of our Research and Development and Orphan Drug tax credit carryforwards over the next three years.

We continue to maintain a full valuation allowance of $234.2 million against all of Akcea's net deferred tax assets and the net state deferred tax assets of Ionis at December 31, 2018 due to uncertainties related to our ability to realize the tax benefits associated with these assets.

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

We 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 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 (lease liability) and an asset representing the underlying leased asset (right of use asset). The new accounting guidance requires us to determine if our leases are operating or financing leases. We will record expense for operating 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. We adopted this guidance on January 1, 2019 and adjusted our opening balance sheet on that date. We elected the available practical expedients. The most significant impact was the recognition of right of use assets and lease liabilities for our operating leases. We are in the process of finalizing the impact of the adoption. The adoption will not have an impact on our consolidated statement of operations or statement of cash flows.

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

In February 2018, the FASB issued updated guidance for reclassification of tax effects from accumulated other comprehensive income (loss). The updated guidance gives entities an option to reclassify amounts included in accumulated other comprehensive income (loss) that under the Tax Act do not have a way to be relieved, and allows a one-time reclassification to retained earnings. The updated guidance is effective for all entities for fiscal years beginning after December 31, 2018, and interim periods within those fiscal years. We have decided not to record the reclassification adjustments provided by this guidance.

In June 2018, the FASB issued updated guidance to simplify the accounting for stock-based compensation expense for nonemployees. Specifically, we are now expensing grants to nonemployees in a similar manner as grants to employees. Previously, we had to re-value these grants at each reporting period to reflect the current fair value. Under the amended guidance, we value grants to nonemployees when we grant them and we will not adjust their value for future changes. We adopted this guidance in the second quarter of 2018. The updated guidance did not have a material impact to our financial results.

In November 2018, the FASB issued clarifying guidance of the interaction between the collaboration accounting guidance and the new revenue recognition guidance we adopted on January 1, 2018 (Topic 606). The clarifying guidance included the following:

1) When a participant is considered a customer in a collaborative arrangement, all of the associated accounting under Topic 606 should be applied;
2) Adds “unit of account” concept to collaboration accounting guidance to align with Topic 606. This is used to determine if revenue is recognized or if a contra expense is recognized from consideration received under a collaboration; and
3) Precludes revenue from being recognized under Topic 606 when a transaction with a collaborative partner is determined not be a customer and is not directly related to the sales to third parties.

The updated guidance is effective for public entities for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. Early adoption is permitted. We plan to adopt this guidance on January 1, 2020. We are currently assessing the effects it will have on our consolidated financial statements and disclosures.

2. Investments

As of December 31, 2018, 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, 2018:

One year or less	77%
After one year but within two years	20%
After two years but within three and one half years	3%
Total	100%

As illustrated above, at December 31, 2018, 97 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, 2018, we had an ownership interest of less than 20 percent in four private companies and two public companies with which we conduct business. The privately-held companies are Atlantic Pharmaceuticals Limited, Dynacure SAS, Seventh Sense Biosystems and Suzhou Ribo Life Science Co, Ltd.The publicly traded companies are ATL and ProQR.

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

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

December 31, 2017	Cost (1)	Gross Unrealized Gains	Gross Unrealized Losses	Estimated 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

(1) We hold our available-for-sale securities at amortized cost.

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

(3) We recognize our equity securities at cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer on our consolidated balance sheet.

Investments we consider to be temporarily impaired at December 31, 2018 are as follows (in thousands):

		Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	546	$ 1,000,461	$ (1,936)	$ 126,357	$ (1,208)	$ 1,126,818	$ (3,144)
Debt securities issued by U.S. government agencies	50	161,312	(109)	34,403	(104)	195,715	(213)
Debt securities issued by the U.S. Treasury	36	183,212	(100)	1,413	(1)	184,625	(101)
Debt securities issued by states of the U.S. and political subdivisions of the states	49	13,868	(14)	62,883	(596)	76,751	(610)
Total temporarily impaired securities	681	$ 1,358,853	$ (2,159)	$ 225,056	$ (1,909)	$ 1,583,909	$ (4,068)

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,	
	2018	2017
1 percent convertible senior notes	$ 568,215	$ 533,111
Long-term mortgage debt	59,842	59,771
Principal balance of fixed rate note with Morgan Stanley (1)	12,500	12,500
Leases and other obligations	6,163	2,095
Total	$ 646,720	$ 607,477
Less: current portion	(13,749)	(1,621)
Total Long-Term Obligations	$ 632,971	$ 605,856

(1) Our $12.5 million fixed rate note with Morgan Stanley is included in our current portion of long-term obligations on our consolidated balance sheet at December 31, 2018.

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, 2018, we had a nominal amount of our 2¾ percent convertible senior notes outstanding. At December 31, 2018, 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 years ended December 31, 2018, 2017 and 2016 included $35.2 million, $32.5 million and $25.1 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,	
	2018	2017
Fair value of outstanding notes	$ 724,966	$ 727,420
Principal amount of convertible notes outstanding	$ 685,450	$ 685,450
Unamortized portion of debt discount	$ 110,817	$ 144,112
Long-term debt	$ 568,215	$ 533,111
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, 2018, 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.

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, 2018 are as follows (in thousands):

2019	$ 22,067
2020	9,330
2021	694,774
2022	2,809
2023	3,494
Thereafter	68,108
Subtotal	$ 800,582
Less: current portion	(12,890)
Less: fixed and determinable interest	(41,837)
Less: unamortized portion of debt discount	(111,426)
Plus: Deferred rent	4,960
Total	$ 639,389

Operating Leases

Ionis Leases

We lease a facility adjacent to our manufacturing facility that has laboratory and office space that we use to support our manufacturing facility. We lease this space under a non-cancelable operating lease with an initial term ending in June 2021 and an option to extend the lease for up to two five-year periods.

Additionally, we lease office space that we sublease to Akcea. We lease this space under a non-cancelable operating lease with an initial term ending in June 2023 and an option to extend the lease for one five-year period. The sublease with Akcea is eliminated in our consolidated financial statements. We also lease office equipment under non-cancelable operating leases with terms through January 2021.

Akcea Lease

On April 5, 2018, Akcea entered into an operating lease agreement for office space located in Boston, Massachusetts for its new corporate headquarters. The lease commencement date was August 15, 2018 and Akcea took occupancy in September 2018. Akcea is leasing this space under a non-cancelable operating lease with an initial term ending after 123 months and an option to extend the lease for an additional five-year term. Under the lease agreement, Akcea received a three-month free rent period, which commenced on August 15, 2018, and a tenant improvement allowance up to $3.8 million. Akcea provided the lessor with a letter of credit to secure its obligations under the lease in the initial amount of $2.4 million, to be reduced to $1.8 million on the third anniversary of the rent commencement date and to $1.2 million on the fifth anniversary of the rent commencement date if Akcea meets certain conditions set forth in the lease at each such time. The letter of credit amount is included in deposits and other assets in our consolidated balance sheet.

Annual future minimum payments under our operating leases as of December 31, 2018 are as follows (in thousands):

	Operating Leases
2019	$ 3,129
2020	3,008
2021	2,725
2022	2,539
2023	2,505
Thereafter	11,862
Total minimum payments	$ 25,768

Rent expense was $2.6 million, $1.7 million and $2.0 million for the years ended December 31, 2018, 2017 and 2016. We recognized rent expense on a straight line basis over the lease term for the lease on our building adjacent to our manufacturing facility, the office building that Akcea subleases and Akcea's office space, which resulted in a deferred rent balance of $5.0 million and $0.1 million at December 31, 2018 and 2017, 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, 2018, 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, 2018.

Common Stock

At December 31, 2018 and 2017, we had 300,000,000 shares of common stock authorized, of which 137,928,828 and 124,976,373 were issued and outstanding, respectively. As of December 31, 2018, total common shares reserved for future issuance were 14,839,373.

During the years ended December 31, 2018, 2017 and 2016, we issued 1,451,000, 1,709,000 and 1,285,000 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 $27.9 million, $22.9 million and $13.7 million in 2018, 2017 and 2016, 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, 2018, a total of 848,753 options were outstanding, of which options to purchase 831,656 shares were exercisable, and 42,925 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, 2018, a total of 9,705,441 options were outstanding, of which 4,801,904 were exercisable, 1,183,154 restricted stock unit awards were outstanding, and 3,340,351 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. In addition, we implemented a change of control and severance benefit plan that provides for change of control and severance benefits to our executive officers, including our chief executive officer and chief financial officer. If we terminate one of our executive officers or if an executive officer resigns for good reason during the period that begins three months before and ends twelve months following a change in control of the company, the impacted executive officers' stock options and RSUs vesting will accelerate for options and RSUs outstanding as of the termination date.

Corporate Transactions and Change in Control under 2011 Plan

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

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

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options and restricted stock units to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan, or the 2002 Plan. In June 2015, after receiving approval from our stockholders, we amended our 2002 Non-Employee Directors Stock Option Plan to increase the total number of shares reserved for issuance. We increased the shares available under our 2002 Non-Employee Directors Stock Option Plan from 1,200,000 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, 2018, a total of 757,750 options were outstanding, of which 437,750 were exercisable, 63,099 restricted stock unit awards were outstanding, and 420,762 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 3,674,596 shares authorized under the plan as of December 31, 2018. 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 2018, employees purchased and we issued to employees 43,416 shares under the ESPP at a weighted average price of $39.03 per share. At December 31, 2018, there were 774,816 shares available for purchase under the ESPP.

Stock Option Activity

The following table summarizes the stock option activity under our stock plans for the year ended December 31, 2018 (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, 2017	9,397	$ 44.52		
Granted	3,518	$ 48.40		
Exercised	(1,064)	$ 17.78		
Cancelled/forfeited/expired	(540)	$ 52.47		
Outstanding at December 31, 2018	11,311	$ 47.85	4.41	$ 93,663
Exercisable at December 31, 2018	6,071	$ 46.83	3.22	$ 63,756

The weighted-average estimated fair values of options granted were $25.49, $25.42 and $26.72 for the years ended December 31, 2018, 2017 and 2016, respectively. The total intrinsic value of options exercised during the years ended December 31, 2018, 2017 and 2016 were $34.8 million, $49.5 million and $28.0 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $18.9 million, $21.2 million and $12.6 million for the years ended December 31, 2018, 2017 and 2016, respectively. For the year ended December 31, 2018, the weighted-average fair value of options exercised was $50.50. As of December 31, 2018, total unrecognized compensation cost related to non-vested stock-based compensation plans was $118.3 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, 2018 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2017	863	$ 49.55
Granted	789	$ 51.06
Vested	(324)	$ 50.21
Cancelled/forfeited	(82)	$ 51.59
Non-vested at December 31, 2018	1,246	$ 50.20

For the years ended December 31, 2018, 2017 and 2016, the weighted-average grant date fair value of RSUs granted was $51.06, $48.88 and $41.79 per RSU, respectively. As of December 31, 2018, total unrecognized compensation cost related to RSUs was $27.9 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 1.4 years.

Stock-based Compensation Expense and Valuation Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2018, 2017 and 2016 (in thousands), which was allocated as follows and includes $44.3 million, $17.5 million and $10.1 million of stock-based compensation expense for Akcea employees in 2018, 2017 and 2016, respectively:

	Year Ended December 31,		
	2018	2017	2016
Cost of products sold	$ 160	$ —	$ —
Research, development and patent	76,557	64,521	55,099
Selling, general and administrative	54,595	21,454	17,009
Total	$ 131,312	$ 85,975	$ 72,108

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, 2018, 2017 and 2016, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	December 31,		
	2018	2017	2016
Risk-free interest rate	2.4%	1.8%	1.5%
Dividend yield	0.0%	0.0%	0.0%
Volatility	63.0%	65.9%	58.7%
Expected life	4.6 years	4.5 years	4.5 years

Board of Director Stock Options:

	December 31,		
	2018	2017	2016
Risk-free interest rate	2.8%	2.2%	1.3%
Dividend yield	0.0%	0.0%	0.0%
Volatility	61.5%	61.2%	53.1%
Expected life	6.6 years	6.6 years	6.5 years

ESPP:

	December 31,		
	2018	2017	2016
Risk-free interest rate	1.8%	0.8%	0.4%
Dividend yield	0.0%	0.0%	0.0%
Volatility	47.3%	59.9%	86.4%
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.

In addition to our stock plans, Akcea has its own stock plan under which it grants options and RSUs and under which it derives its stock-based compensation expense. The following are the weighted-average Black-Scholes assumptions Akcea used under its plan for the years ended December 31, 2018, 2017 and 2016:

Employee Stock Options:

	December 31,		
	2018	2017	2016
Risk-free interest rate	2.8%	1.9%	1.6%
Dividend yield	0.0%	0.0%	0.0%
Volatility	77.1%	79.5%	71.4%
Expected life	6.08 years	6.06 years	6.08 years

Board of Director Stock Options:

	December 31,		
	2018	2017	2016
Risk-free interest rate	2.9%	1.9%	2.0%
Dividend yield	0.0%	0.0%	0.0%
Volatility	78.2%	79.4%	79.6%
Expected life	6.42 years	6.25 years	6.08 years

The following summarizes the Black-Scholes input methodology for Akcea options that differs from the methodology we use for Ionis options:

Volatility. Since Akcea does not have sufficient history to estimate the volatility of its common stock, Akcea calculates its expected volatility based on a blend of its historical volatility and reported data from selected publicly traded peer companies for which historical information is available. Akcea plans to continue to use this blend to calculate its volatility until the historical volatility of its common stock is sufficient to measure expected volatility for future option grants.

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

5. Income Taxes

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

	Year Ended December 31,		
	2018	2017	2016
United States	$ (69,576)	$ (5,289)	$ (57,466)
Foreign	(6,580)	(11,474)	—
Loss before income tax (benefit) expense	$ (76,156)	$ (16,763)	$ (57,466)

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

	Year Ended December 31,		
	2018	2017	2016
Current:			
Federal	$ 438	$ (7,460)	$ 1,067
State	(1,442)	1,246	1,867
Foreign	374	234	—
Total current income tax (benefit) expense	(630)	(5,980)	2,934
Deferred:			
Federal	(290,511)	—	—
State	—	—	—
Total deferred income tax (benefit) expense	(290,511)	—	—
Total income tax (benefit) expense	$ (291,141)	$ (5,980)	$ 2,934

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

	Year Ended December 31,					
	2018		2017		2016	
Pre-tax loss	$ (76,156)		$ (16,763)		$ (57,466)	
Statutory rate	(15,993)	21.0%	(5,867)	35.0%	(20,113)	35.0%
State income tax net of federal benefit	(2,202)	2.9%	820	(4.9)%	95	(0.2)%
Foreign	1,735	(2.3)%	4,299	(25.6)%	—	0.0%
Net change in valuation allowance	(277,924)	364.9%	(86,296)	514.8%	46,402	(80.7)%
Net operating loss expiration	8,864	(11.6)%	3,987	(23.8)%	—	0.0%
TEGSEDI licensing gain	59,583	(78.2)%	—	0.0%	—	0.0%
Tax credits	(73,362)	96.3%	(32,769)	195.5%	(26,954)	46.9%
Deferred tax true-up	9,947	(13.1)%	4,848	(28.9)%	2,591	(4.5)%
Tax rate change	(1,808)	2.4%	114,832	(685.0)%	—	0.0%
Non-deductible compensation	3,154	(4.1)%	1,575	(9.4)%	825	(1.4)%
Other non-deductible items	(569)	0.7%	2,548	(15.2)%	324	(0.6)%
Akcea deconsolidation adjustment at IPO	—	0.0%	469	(2.8)%	—	0.0%
Stock-based compensation	(4,199)	5.5%	(14,337)	85.5%	—	0.0%
Other	1,633	(2.1)%	(89)	0.5%	(236)	0.4%
Effective rate	$ (291,141)	382.3%	$ (5,980)	35.7%	$ 2,934	(5.1)%

Significant components of our deferred tax assets and liabilities as of December 31, 2018 and 2017 are as follows (in thousands):

	Year Ended December 31,	
	2018	2017
Deferred Tax Assets:		
Net operating loss carryovers	$ 89,717	$ 153,575
R&D credits	313,652	240,290
Deferred revenue	27,381	54,302
Stock-based compensation	61,027	40,090
Intangible and capital assets	49,007	672
Other	8,275	12,164
Total deferred tax assets	$ 549,059	$ 501,093
Deferred Tax Liabilities:		
Convertible debt	$ (24,018)	$ (32,391)
Net deferred tax asset	$ 525,041	$ 468,702
Valuation allowance	(234,245)	(468,702)
Total net deferred tax assets and liabilities	$ 290,796	$ —

We have adjusted all prior year tax amounts to reflect the tax impact of our adoption of Topic 606.

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

We have historically recorded a valuation allowance against all our net deferred tax assets due to cumulative financial statement losses. However, in the fourth quarter of 2018, we reversed the valuation allowance previously recorded against Ionis' stand-alone U.S. federal net deferred tax assets, resulting in a one-time non-cash tax benefit of $332.1 million. Given our current stand-alone Ionis pre-tax income, and assuming we maintain this current level of Ionis stand-alone pre-tax income, we expect to generate income before taxes in the U.S. in future periods at a level that would result in us fully utilizing our U.S. federal net operating loss carryforwards and most of our Research and Development and Orphan Drug tax credit carryforwards over the next three years.

We continue to maintain a full valuation allowance of $234.2 million against all of Akcea's net deferred tax assets and the net state deferred tax assets of Ionis at December 31, 2018 due to uncertainties related to our ability to realize the tax benefits associated with these assets.

Our valuation allowance decreased by $234.5 million from December 31, 2017 to December 31, 2018. The net decrease relates primarily to the reversal of the valuation allowance previously recorded against Ionis' stand-alone U.S. federal net deferred tax assets, offset by current year utilization of a portion of our net operating loss carry forwards.

At December 31, 2018, we had federal and state, primarily California, tax net operating loss carryforwards of $284.6 million and $808.7 million, respectively. Our federal tax loss carryforwards will begin to expire in 2033, unless we use them before then. Our California loss carryforwards continued to expire in 2018. At December 31, 2018, we also had federal and California research and development tax credit carryforwards of $288.9 million and $68.4 million, respectively. Our Federal research and development tax credit carryforwards began 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.

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cuts and Jobs Act of 2017, or the Tax Act. The Tax Act made broad and complex changes to the U.S. tax code, including, but not limited to, reducing the U.S. federal corporate income tax rate to 21 percent, imposing a mandatory one-time transition tax on certain unrepatriated earnings of foreign subsidiaries and eliminating the corporate alternative minimum tax, or AMT, and changing how existing AMT credits can be realized. We were required to recognize the tax effect of the tax law changes the year of enactment. In order to calculate these effects, we were required to determine the transition tax amount, remeasure our U.S. deferred tax assets and liabilities, and consider the impact to our AMT tax credit carryforwards. For the year ended December 31, 2017, we recorded provisional amounts in accordance with that guidance where it was possible for us to make reasonable estimates of the effects of the Tax Act. We evaluated the decrease in our corporate tax rate and recorded a provisional, one-time tax expense of $107.3 million at December 31, 2017. We fully offset our tax effect by a decrease in our valuation allowance which resulted in no net tax effect in 2017. During the fourth quarter of 2018, we completed our accounting for all aspects of the Tax Act. We did not identify material changes from our 2017 provisional analysis.

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,		
	2018	2017	2016
Beginning balance of unrecognized tax benefits	$ 78,014	$ 66,999	$ 51,257
Settlement of prior period tax positions	—	—	(4,033)
Decrease for prior period tax positions	(12,814)	—	—
Increase for prior period tax positions	—	1,520	7,928
Increase for current period tax positions	3,101	9,495	11,847
Ending balance of unrecognized tax benefits	$ 68,301	$ 78,014	$ 66,999

Included in the balance of unrecognized tax benefits at December 31, 2018, is $55.5 million that could impact our effective tax rate, subject to our remaining valuation allowance.

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

We recognize interest and/or penalties related to income tax matters in income tax expense. We did not recognize any accrued interest and penalties related to gross unrecognized tax benefits during the year ended December 31, 2018.

We are subject to taxation in the U.S. and various state and foreign jurisdictions. Our tax years for 1999 through 2018 are subject to examination by the U.S. federal, state and foreign tax authorities.

We do not provide for a U.S. income tax liability and foreign withholding taxes on undistributed foreign earnings of our foreign subsidiaries as we consider those earnings to be permanently reinvested. It is not practicable for us to calculate the amount of unrecognized deferred tax liabilities associated with these earnings.

We are subject to periodic audits by domestic and foreign tax authorities; however, we are not aware of any audits at this time. We believe that we have appropriate support for the income tax positions taken on our tax returns and our accruals for tax liabilities are adequate for all open audit years. Our conclusions are based on an assessment of many factors, including past experience and interpretations of tax law applied to the facts of each matter.

6. Collaborative Arrangements and Licensing Agreements

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. In December 2017, we entered into a collaboration with Biogen to identify new antisense medicines for the treatment of SMA. Additionally, we and Biogen are currently developing six other medicines to treat neurodegenerative diseases under these collaborations, including IONIS-SOD1$_{Rx}$ for ALS, IONIS-MAPT$_{Rx}$ for Alzheimer's disease, IONIS-C9$_{Rx}$ for ALS, and IONIS-BIIB6$_{Rx}$, IONIS-BIIB7$_{Rx}$ and IONIS-BIIB8$_{Rx}$ to treat undisclosed neurodegenerative diseases. In addition to these medicines, we and Biogen are evaluating numerous additional targets to develop medicines to treat neurological diseases. In April 2018, we entered into a new strategic collaboration for the treatment of neurological diseases with Biogen. From inception through December 2018, we have received over $2.0 billion from our Biogen collaborations, including $1 billion we received from Biogen in the second quarter of 2018 for our 2018 strategic neurology collaboration.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. Biogen reported in January 2019 that SPINRAZA was approved in over 40 countries around the world. In February 2019, SPINRAZA was approved in China. Biogen is responsible for global SPINRAZA commercial activities.

From inception through December 2018, we earned more than $785 million in total revenue under our SPINRAZA collaboration, including more than $350 million in revenue from SPINRAZA royalties and more than $435 million in R&D revenue. We are receiving tiered royalties ranging from 11 percent to 15 percent on any net sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on net sales of SPINRAZA. Biogen is responsible for all further global development, regulatory and commercialization activities and costs for SPINRAZA.

Over the course of our SPINRAZA collaboration, we identified two performance obligations, which were to perform R&D services and to deliver the SPINRAZA license to Biogen. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance through December 2016. We recognized the $75 million license fee for SPINRAZA as revenue when we delivered the license to Biogen in July 2016 because Biogen had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Biogen.

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

New antisense medicines for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen 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. We will receive development and regulatory milestone payments from Biogen if new medicines advance towards marketing approval. In total over the term of our collaboration, we are eligible to receive up to $1.2 billion in license fees, milestone payments and other payments, including up to $80 million for the achievement of development milestones, up to $180 million for the achievement of commercialization milestones and up to $800 million for the achievement of sales milestones. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales. We will achieve the next payment of up to $60 millionfor the license of a medicine under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined the transaction price to be the $25 million upfront payment we received when we entered into the collaboration. We allocated the transaction price to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in December 2020.

Neurology Collaborations

2018 Strategic Neurology

In April 2018, we and Biogen entered into a new strategic collaboration to develop novel antisense medicines for a broad range of neurological diseases and entered into a SPA. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for these diseases for 10 years. We are responsible for the identification of antisense drug candidates based on selected targets. Biogen is responsible for conducting IND-enabling toxicology studies for the selected target. Biogen will have the option to license the selected target after it completes the IND-enabling toxicology study. If Biogen exercises its option for a medicine, it will assume all further global development, regulatory and commercialization responsibilities and costs for that medicine.

In the second quarter of 2018, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at an approximately 25 percent cash premium and $375 million in an upfront payment. We are eligible to receive up to $270 million in milestone payments for each medicine that achieves marketing approval. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales. From inception through December 2018, we have received over $1 billion in payments under this collaboration, including $15 million we received in the fourth quarter of 2018 for advancing two targets under this collaboration. We will achieve the next payment of $7.5 million if Biogen designates a target under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined our transaction price to be $552 million, comprised of $375 million from the upfront payment and $177 million for the premium paid by Biogen for its purchase of our common stock. We determined the fair value of the premium we received by using the stated premium in the SPA and applying a lack of marketability discount. We included a lack of marketability discount in our valuation of the premium because Biogen received restricted shares. We allocated the transaction price to our single performance obligation. In the fourth quarter of 2018, we received $15 million in milestone payments when we advanced two targets under this collaboration. We added these payments to our transaction price for our R&D services performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in June 2028.

2013 Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license medicines resulting from this collaboration. We will usually be responsible for drug discovery and early development of antisense medicines and Biogen will have the option to license antisense medicines after Phase 2 proof of concept. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option for a medicine, it will assume all further global development, regulatory and commercialization responsibilities and costs for that medicine. We are currently advancing five medicines, IONIS-$SOD1_{Rx}$, IONIS-$C9_{Rx}$, IONIS-$BIIB6_{Rx}$, IONIS-$BIIB7_{Rx}$ and IONIS-$BIIB8_{Rx}$ under this collaboration. In the fourth quarter of 2018, Biogen licensed IONIS-$SOD1_{Rx}$, and as a result Biogen now is responsible for all further global development, regulatory and commercialization activities and costs for IONIS-$SOD1_{Rx}$.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all medicines developed 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 per program. The $260 million per program consists of approximately $60 million in development milestones, including amounts related to the cost of clinical trials, and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any antisense medicines developed under this collaboration. From inception through December 2018, we have received over $210 million in upfront fees, milestone payments and other payments under this collaboration, not including a $5 million milestone payment we earned in the fourth quarter of 2018 for Biogen's initiation of a Proof of Concept study for IONIS-$SOD1_{Rx}$ which we received in the first quarter of 2019. We will achieve the next payment of up to $10 million if we advance a program under this collaboration.

At the commencement of our strategic neurology collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. At inception, we determined the transaction price to be the $100 million upfront payment we received and allocated it to our single performance obligation. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. We are recognizing revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in September 2019. From inception through December 2018, we have included $145 million in total payments in the transaction price for our R&D services performance obligation. In the third quarter of 2018, we earned a $10 million milestone payment when Biogen initiated a Phase 1 study of IONIS-$C9_{Rx}$. We concluded that the milestone payment was not related to our R&D services performance obligation. Therefore, we recognized this milestone payment in full in the third quarter of 2018 because we do not have any performance obligations related to this milestone payment.

We identified a second performance obligation upon Biogen's license of IONIS-$SOD1_{Rx}$ in the fourth quarter of 2018 because the license we granted to Biogen is distinct from our other performance obligation. We recognized the $35 million license fee for IONIS-$SOD1_{Rx}$ as revenue at that time because Biogen had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Biogen. Additionally, in the fourth quarter of 2018 we earned a $5 million milestone when Biogen initiated a Proof-of-Concept study for IONIS-$SOD1_{Rx}$. We concluded that the milestone payment was not related to our R&D services performance obligation. Therefore, we recognized this milestone payment in full in the fourth quarter of 2018 because we do not have any performance obligations related to this milestone payment.

Neurology

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

Under the terms of the agreement, we received an upfront payment of $30 million. Over the term of the collaboration, we are eligible to receive up to $210 million in a license fee and milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. The $210 million per program consists of up to $10 million in development milestone payments, plus a mark-up on the cost estimate of the Phase 1 and 2 studies and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales of any medicines resulting from each of the three programs. From inception through December 2018, we have received $58 million in milestone payments and upfront fees under this collaboration. We will achieve the next payment of $7.5 million if we continue to advance IONIS-$MAPT_{Rx}$.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. At inception, we determined the transaction price to be the $30 million upfront payment we received and allocated it to our single performance obligation. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in December 2020. From inception through December 2018, we have included $40 million in total payments in the transaction price for our R&D services performance obligation.

During the years ended December 31, 2018, 2017 and 2016, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Years Ended December 31,		
	2018	2017	2016
		(as revised)	
SPINRAZA royalties (commercial revenue)	$ 237.9	$ 112.5	$ 0.9
R&D revenue	137.1	150.6	248.8
Total revenue from our relationship with Biogen	375.0	263.1	249.7
Percentage of total revenue	63%	51%	67%

Our consolidated balance sheet at December 31, 2018 and 2017 included deferred revenue of $580.9 million and $93.6 million, respectively, related to our relationship with Biogen.

Research, Development and Commercialization Partners

AstraZeneca

Cardiac, Renal and Metabolic Diseases Collaboration

In July 2015, we and AstraZeneca formed a collaboration to discover and develop antisense therapies for treating cardiac, renal and metabolic diseases. Under our collaboration, AstraZeneca has licensed three medicines from us: IONIS-AZ4-2.5-L_{Rx}, a medicine we designed to treat cardiovascular disease and our first medicine that combines our Generation 2.5 and LICA technology, IONIS-AZ5-2.5$_{Rx}$, a medicine we designed to treat a genetically associated form of kidney disease and IONIS-AZ6-2.5-L_{Rx}, a medicine we designed to inhibit an undisclosed target to treat patients with nonalcoholic steatohepatitis, or NASH. AstraZeneca is responsible for all further global development, regulatory and commercialization activities and costs for each of the medicines it has licensed and any other future medicines AstraZeneca licenses.

Under the terms of the agreement, we received a $65 million upfront payment. We are eligible to receive license fees and milestone payments of up to more than $4 billion as medicines under this collaboration advance, including up to $1.1 billion for the achievement of development milestones and up to $2.9 billion for regulatory milestones. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. From inception through December 2018, we have received over $165 million in upfront fees, license fees, milestone payments, and other payments under this collaboration, including a $10 million milestone payment we earned in the third quarter of 2018 when AstraZeneca initiated a Phase 1 trial for IONIS-AZ4-2.5-L_{Rx}. We will achieve the next payment of $10 million under this collaboration if we advance a medicine under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for AstraZeneca. We determined the transaction price to be the $65 million upfront payment we received and we allocated it to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy this performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy this performance obligation in August 2021. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. From inception through December 2018, we have included $90 million in payments in the transaction price for our R&D services performance obligation.

We identified separate performance obligations upon AstraZeneca's license of IONIS-AZ5-2.5$_{Rx}$ and IONIS-AZ6-2.5-L_{Rx} in the first quarter of 2018 because the licenses are distinct from our other performance obligation and each other. We recognized each $30 million license fee in the first quarter of 2018 because AstraZeneca had full use of the licenses without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the licenses after we delivered them to AstraZeneca.

In the third quarter of 2018, we earned a $10 million milestone payment when AstraZeneca initiated a Phase 1 study of IONIS-AZ4-2.5-L_{Rx}. We concluded that the milestone payment was not related to our R&D services performance obligation. Therefore, we recognized this milestone payment in full in the third quarter of 2018 because we do not have any performance obligations related to this milestone payment.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense medicines to treat cancer. As part of the agreement, we granted AstraZeneca an exclusive license to develop and commercialize danvatirsen (formerly IONIS-STAT3-2.5$_{Rx}$) for the treatment of cancer. AstraZeneca is now responsible for all global development, regulatory and commercialization activities for danvatirsen. We and AstraZeneca have evaluated danvatirsen in people with head and neck cancer, advanced lymphoma and advanced metastatic hepatocellular carcinoma. AstraZeneca is evaluating danvatirsen in combination with durvalumab, AstraZeneca's PD-L1 blocking drug, in people with head and neck cancer, metastatic bladder cancer and metastatic non-small cell lung cancer. We and AstraZeneca also established an oncology research program. AstraZeneca has the option to license medicines resulting from the program, and if AstraZeneca exercises its option for a medicine, it will be responsible for all further global development, regulatory and commercialization activities and costs for such medicine. In the fourth quarter of 2018, we added IONIS-AZ7-2.5$_{Rx}$ to our preclinical pipeline, a second drug under our oncology collaboration.

Under the terms of this agreement, we received $31 million in upfront payments. We are eligible to receive milestone payments and license fees from AstraZeneca as programs advance in development. If AstraZeneca successfully develops danvatirsen and another medicine under the research program, we could receive license fees and milestone payments of up to more than $450 million, including up to $152 million for the achievement of development milestones and up to $275 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any medicines resulting from these programs. From inception through December 2018, we have received over $125 million in upfront fees, milestone payments, and other payments under this oncology collaboration, including nearly $30 million in milestone payments we achieved when AstraZeneca advanced danvatirsen and IONIS-AZ7-2.5$_{Rx}$, in the fourth quarter of 2018. We will achieve the next payment of up to $25 million if we advance a medicine under our cancer research program with AstraZeneca.

At the commencement of this collaboration, we identified four performance obligations. We determined the transaction price to be the $31 million upfront payments we received. We allocated the transaction price based on the estimated stand-alone selling price of each of our performance obligations and recognized the associated revenue over the period of our performance. We recognized revenue for three of our obligations over our period of performance, which concluded in March 2014. Our remaining performance obligation was to perform R&D services. We allocated $7.6 million to this performance obligation and recognized the associated revenue over the period of our performance, which ended in February 2018. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation.

In the fourth quarter of 2018, we earned a $17.5 million milestone payment and a $10 million milestone payment when AstraZeneca advanced two programs under our collaboration. We recognized these milestone payments in full in the fourth quarter because we do not have any performance obligations related to these milestone payments.

During the years ended December 31, 2018, 2017 and 2016, we earned the following revenue from our relationship with AstraZeneca (in millions, except percentage amounts):

	Years Ended December 31,		
	2018	2017	2016
		(as revised)	
R&D revenue	$ 120.7	$ 21.6	$ 41.3
Percentage of total revenue	20%	4%	11%

Our consolidated balance sheet at December 31, 2018 and 2017 included deferred revenue of $40.1 million and $57.7 million, respectively, related to our relationship with AstraZeneca.

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. We were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis. Under the terms of the agreement, we received a $100 million upfront payment in the second quarter of 2015. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of IONIS-FXI-L$_{Rx}$, which Bayer licensed. In conjunction with the decision to advance these programs, we received a $75 million payment from Bayer. We are conducting a Phase 2b study evaluating IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis to finalize dose selection. Additionally, we are developing 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 medicines.

We are eligible to receive additional milestone payments as each medicine advances toward the market. In total over the term of this collaboration, we are eligible to receive up to $385 million in license fees, milestone payments and other payments, including up to $125 million for the achievement of development milestones and up to $110 million for the achievement of commercialization milestones. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of both medicines combined. From inception through December 2018, we have received over $175 million from our Bayer collaboration. We will achieve the next payment of $10 million if a program advances under this collaboration.

At the commencement of this collaboration, we identified three performance obligations. We determined the transaction price to be the $100 million upfront payment we received. We allocated the transaction price based on the relative stand-alone selling prices of each of our performance obligations and recognized the associated revenue as follows:

- We recognized $91.2 million for the exclusive license of IONIS-FXI$_{Rx}$ in May 2015 because Bayer had full use of the license without any continuing involvement from us.
- We recognized $4.3 million for the R&D services for IONIS-FXI$_{Rx}$ over the period of our performance, which ended in November 2016.
- We allocated $4.5 million for API, which we are recognizing into revenue as we deliver the API.

In February 2017, when we amended our collaboration with Bayer, we identified two new performance obligations, one for the license of IONIS-FXI-L$_{Rx}$ and one for R&D services. We determined the transaction price to be the $75 million payment. We allocated $64.9 million to the license of IONIS-FXI-L$_{Rx}$ based on its estimated stand-alone selling price and recognized the associated revenue upon our delivery of the license in the first quarter of 2017. We allocated $10.1 million to our R&D services performance obligation based on an estimated stand-alone selling price. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our R&D services performance obligation in May 2019.

During the years ended December 31, 2018, 2017 and 2016, we earned the following revenue from our relationship with Bayer (in millions, except percentage amounts):

	Years Ended December 31,		
	2018	2017	2016
		(as revised)	
R&D revenue	$ 5.0	$ 67.1	$ 5.4
Percentage of total revenue	1%	13%	1%

Our consolidated balance sheet at December 31, 2018 and 2017 included deferred revenue of $4.3 million and $9.3 million, respectively, related to our relationship with Bayer.

GSK

In March 2010, we entered into an alliance with GSK using our antisense drug discovery platform to discover and develop new medicines against targets for rare and serious diseases, including infectious diseases and some conditions causing blindness. Under the terms of the agreement, we received upfront payments of $35 million.

GSK is advancing two medicines 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 medicines, which we designed to reduce the production of viral proteins associated with HBV infection. GSK has the exclusive option to license the medicines resulting from this alliance at Phase 2 proof-of-concept for a license fee.

Under our agreement, if GSK successfully develops these medicines and achieves pre-agreed sales targets, we could receive license fees and 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. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that GSK successfully commercializes under this alliance. From inception through December 2018, we have received more than $162 million in payments under this alliance with GSK. We will achieve the next payment of up to $25 million if GSK licenses a medicine under this program.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for GSK. We determined the transaction price to be the $35 million upfront payments we received and allocated it to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, which ended in March 2015. We do not have any remaining performance obligations under our collaboration with GSK, however we can still earn additional payments and royalties as GSK advances these medicines.

During the years ended December 31, 2018, 2017 and 2016, we earned the following revenue from our relationship with GSK (in millions, except percentage amounts):

	Years Ended December 31,		
	2018	2017	2016
		(as revised)	
R&D revenue	$ 1.6	$ 14.8	$ 17.5
Percentage of total revenue	0%	3%	5%

We did not have any deferred revenue from our relationship with GSK at December 31, 2018 or December 31, 2017.

Janssen Biotech, Inc.

In December 2014, we entered into a collaboration agreement with Janssen Biotech, Inc. to discover and develop antisense medicines that can be locally administered, including oral delivery, to treat autoimmune disorders of the gastrointestinal tract. Janssen has the option to license medicines from us through the designation of a development candidate for up to three programs. Under our collaboration, Janssen licensed IONIS-JBI1-2.5$_{Rx}$ in July 2016 and IONIS-JBI2-2.5$_{Rx}$ in November 2017. Janssen is currently conducting a Phase 1 study of IONIS-JBI1-2.5$_{Rx}$ and IONIS-JBI2-2.5$_{Rx}$ is in preclinical development. Prior to option exercise we are responsible for the discovery activities to identify development candidates. If Janssen exercises an option for any 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. We are eligible to receive up to more than $800 million in license fees and 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 2018, we have received over $75 million, including $15 million in license fees when Janssen licensed IONIS-JBI1-2.5$_{Rx}$ and IONIS-JBI2-2.5$_{Rx}$ from us. 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 net sales from any medicines resulting from this collaboration. We will achieve the next payment of $5 million if Janssen continues to advance a target under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Janssen. We determined the transaction price to be the $35 million upfront payments we received. We allocated the $35 million to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, which ended in November 2017.

We identified separate performance obligations each time Janssen licensed one of our medicines under our collaboration because the licenses we granted to Janssen were distinct from our other performance obligations. We recognized the $10 million license fee for IONIS-JBI1-2.5$_{Rx}$ in July 2016 and $5 million for the license of IONIS-JBI2-2.5$_{Rx}$ in November 2017, because Janssen had full use of the licenses without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the licenses after we delivered them to Janssen.

During the years ended December 31, 2018, 2017 and 2016, we earned the following revenue from our relationship with Janssen (in millions, except percentage amounts):

	Years Ended December 31,		
	2018	2017	2016
		(as revised)	
R&D revenue	$ 6.6	$ 36.0	$ 24.8
Percentage of total revenue	1%	7%	7%

We did not have any deferred revenue from our relationship with Janssen at December 31, 2018 and 2017.

Roche

Huntington's Disease

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for Huntington's disease, or HD, based on our antisense technology. Roche had the option to license the medicines 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 medicine targeting huntingtin, or HTT, protein. We evaluated a medicine targeting HTT, IONIS-HTT$_{Rx}$, in a Phase 1/2 clinical study in people with early stage HD.

In December 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license 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 $30 million in April 2013. In December 2016, we updated development activities for IONIS-HTT$_{Rx}$ and as a result we were eligible for an additional $3 million payment, which we achieved in 2017. We are eligible to receive up to $365 million in a license fee and milestone payments including up to $70 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of commercialization milestones. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional medicine successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on any net sales of any product resulting from this alliance. From inception through December 2018, we have received over $112 million in upfront fees, milestone payments and license fees for advancing IONIS-HTT$_{Rx}$, not including $35 million in milestone payments we earned in the first quarter of 2019 when Roche dosed the first patient in a Phase 3 study for IONIS-HTT$_{Rx}$. We will achieve the next payment of $15 million if Roche advances IONIS-HTT$_{Rx}$.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Roche. We determined the transaction price to be the $30 million upfront payment we received and allocated it to our single performance obligation. As we achieved milestone payments for our R&D services, we included these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation over our period of performance, which ended in September 2017.

We identified a second performance obligation upon Roche's license of IONIS-HTT$_{Rx}$ in the fourth quarter of 2017 because the license we granted to Roche is distinct from our other performance obligation. We recognized the $45 million license fee for IONIS-HTT$_{Rx}$ as revenue at that time because Roche had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Roche.

We do not have any remaining performance obligations related to IONIS-HTT$_{Rx}$ under this collaboration with Roche, however we can still earn additional payments and royalties as Roche advances IONIS-HTT$_{Rx}$.

IONIS-FB-L$_{Rx}$ for Complement-Mediated Diseases

In October 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L$_{Rx}$ for the treatment of complement-mediated diseases. The first indication we plan to pursue is the treatment of patients with Geographic Atrophy, or GA, the advanced stage of dry age-related macular degeneration, or AMD. We are responsible for conducting a Phase 2 study in patients with dry AMD. In addition, we are exploring the medicine in a severe and rare renal indication. Roche has the option to license IONIS-FB-L$_{Rx}$ at the completion of these studies. Upon licensing, Roche will be responsible for all further global development, regulatory and commercialization activities and costs.

Under the terms of this agreement, we received a $75 million upfront payment in October 2018. We are eligible to receive up to $684 million in development, regulatory and sales milestone payments and license fees. In addition, we are also eligible to receive tiered royalties from the high teens to twenty percent on net sales. We will achieve the next payment of $20 million when we advance the Phase 2 study in patients with dry AMD.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Roche. We determined the transaction price to be the $75 million upfront payment we received and allocated it to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in December 2022.

During the years ended December 31, 2018, 2017 and 2016, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	Years Ended December 31,		
	2018	2017	2016
		(as revised)	
R&D revenue	$ 8.3	$ 55.7	$ 10.7
Percentage of total revenue	1%	11%	3%

Our consolidated balance sheet at December 31, 2018 included deferred revenue of $72.6 million related to our relationship with Roche. We did not have any deferred revenue related to our relationship with Roche at December 31, 2017.

Akcea Collaborations

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

Novartis

In January 2017, we and Akcea initiated a collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$. Under the collaboration agreement, Novartis has an exclusive option to further 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 initial quantities of API for each medicine. If Novartis exercises an option for either of these medicines, Novartis will be responsible for all further global development, regulatory and co-commercialization activities and costs for such medicine.

Akcea received a $75 million upfront payment in the first quarter of 2017, of which it retained $60 million and paid us $15 million as a sublicense fee. In February 2019, Novartis licensed AKCEA-APO(a)-L$_{Rx}$ and we earned a $150 million license fee. Akcea will pay us $75 million as a sublicense fee in 2.8 million shares of Akcea common stock. Novartis is responsible for conducting and funding all future development, regulatory and commercialization activities for AKCEA-APO(a)-L$_{Rx}$, including a global pivotal cardiovascular outcomes study, for which planning and initiation activities are underway. If Novartis exercises its option for AKCEA-APOCIII-L$_{Rx}$, Novartis will pay Akcea a license fee equal to $150 million. In addition, for AKCEA-APO(a)-L$_{Rx}$, Akcea is eligible to receive up to $675 million in milestone payments, including $25 million for the achievement of a development milestone, up to $290 million for the achievement of regulatory milestones and up to $360 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L$_{Rx}$, Akcea is eligible to receive up to $530 million in 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 $265 million for the achievement of commercialization milestones. Akcea is also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of AKCEA-APO(a)-L$_{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. In connection with Novartis' license of AKCEA-APO(a)-L$_{Rx}$, Akcea and Novartis established a more definitive framework under which the companies would negotiate the co-commercialization of AKCEA-APO(a)-L$_{Rx}$ in selected markets. Included in this framework is an option by which Novartis could solely commercialize AKCEA-APO(a)-L$_{Rx}$ in exchange for Novartis paying Akcea increased commercial milestone payments based on sales of AKCEA-APO(a)-L$_{Rx}$. Akcea may co-commercialize IONIS-APOCIII-L$_{Rx}$ if licensed and commercialized by Novartis in selected markets through its specialized sales force under terms and conditions to be negotiated with Novartis in the future.

In conjunction with this collaboration, we entered into a SPA with Novartis. As part of the SPA, Novartis purchased 1.6 million shares of our common stock for $100 million in the first quarter of 2017. As part of the SPA, Novartis was required to purchase $50 million of Akcea's common stock at the IPO price or our common stock at a premium if an IPO did not occur by April 2018. Under the SPA, in July 2017, Novartis purchased $50 million of Akcea's common stock in a separate private placement concurrent with the completion of its IPO at a price per share equal to the IPO price.

At the commencement of this collaboration, we identified four separate performance obligations:

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

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

We determined our transaction price to be $108.4 million, comprised of the following:

- $75 million from the upfront payment;
- $28.4 million for the premium paid by Novartis for its purchase of our common stock at a premium in the first quarter of 2017; and
- $5.0 million for the potential premium Novartis would have paid if they purchased our common stock in the future.

We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- $64.0 million for the R&D services for AKCEA-APO(a)-L_{Rx};
- $40.1 million for the R&D services for AKCEA-APOCIII-L_{Rx};
- $1.5 million for the delivery of AKCEA-APO(a)-L_{Rx} API; and
- $2.8 million for the delivery of AKCEA-APOCIII-L_{Rx} API.

We are recognizing revenue related to the R&D services for the AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} performance obligations as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We satisfied the significant portion of our performance obligation for AKCEA-APO(a)-L_{Rx} in December 2018 and we currently estimate we will satisfy the remainder by mid-2019. We currently estimate we will satisfy the significant portion of our performance obligation for AKCEA-APOCIII-L_{Rx} by mid-2020 with the remainder by the end of 2019. We recognized the amount attributed to the API supply for AKCEA-APO(a)-L_{Rx} when we delivered it to Novartis in 2017. We recognized the amount attributed to the API supply for AKCEA-APOCIII-L_{Rx} when we delivered it to Novartis in May 2018.

Akcea is responsible for the development activities under this collaboration. As such, Akcea is recognizing the associated revenue in its statement of operations, and we reflect all of Akcea's revenue in our consolidated results. Akcea pays us sublicense fees for payments that it receives under the collaboration and we recognize those fees as revenue in our Ionis Core operating segment results and Akcea recognizes the fees as R&D expense. In our consolidated results, we eliminate this sublicense revenue and expense. Any cash Akcea receives is included in our consolidated balance sheet.

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

	Years Ended December 31,	
	2018	2017 (as revised)
R&D revenue	$ 50.6	$ 43.4
Percentage of total revenue	8%	8%

Our consolidated balance sheet at December 31, 2018 and 2017 included deferred revenue of $28.8 million and $70.7 million, respectively, related to our relationship with Novartis.

PTC Therapeutics

In August 2018, Akcea entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America. Under the license agreement, Akcea is eligible to receive up to $26 million in payments, including $12 million which it received in the third quarter of 2018, $6 million upon the earlier of FDA or EMA approval of WAYLIVRA and up to $8 million for regulatory milestones. Akcea is eligible to receive royalties from PTC in the mid-20 percent range on net sales in Latin America for each medicine. PTC's obligation to pay Akcea royalties begins on the earlier of 12 months after the first commercial sale of a product in Brazil or the date that PTC recognizes revenue of at least $10 million in Latin America. Consistent with the agreements between Ionis and Akcea, the companies will share all payments, including royalties.

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

Akcea was responsible for the activities under this collaboration. As such, Akcea is recognizing the associated revenue in its statement of operations, and we reflect all of Akcea's revenue in our consolidated results. Akcea pays us sublicense fees for payments that it receives under the collaboration and we recognize those fees as revenue in our Ionis Core operating segment results and Akcea recognizes the fees as SG&A expense. For example, during the third quarter of 2018, we recognized $7.2 million of sublicense revenue in our Ionis Core operating segment results related to our portion of the PTC license fee Akcea paid us. In our consolidated results, we eliminate this sublicense revenue and expense. Any cash Akcea receives is included in our consolidated balance sheet.

Our consolidated balance sheet at December 31, 2018 and 2017 did not include any deferred revenue related to our relationship with PTC.

External Project Funding

We are pursuing discovery and development projects that provide us with new therapeutic applications for antisense medicines. 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. Our External Project Funding partners include the following:

- *CHDI Foundation*- Through our development collaboration, CHDI provided financial and scientific support to our Huntington's disease drug discovery program. We have reimbursed CHDI for its support of our Huntington's disease program out of the payments we receive from Roche.
- *Cystic Fibrosis Foundation*- We received upfront funding from the Cystic Fibrosis Foundation to discover and advance a medicine for the treatment of cystic fibrosis. In exchange for this funding, we are obligated to pay the Cystic Fibrosis Foundation up to $18 million upon achieving specific regulatory and sales events if we advance a medicine under our collaboration.
- *The Ludwig Institute; Center for Neurological Studies*- We have a collaboration with the Ludwig Institute, the Center for Neurological Studies and researchers to discover and develop antisense medicines for ALS and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and the Center for Neurological Studies modest milestone payments and royalties on any antisense medicines resulting from the collaboration.

In-Licensing Agreements

Our in-licensing arrangements include:

- *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 net 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 net sales of SPINRAZA. Additionally, we owe a low single digit royalty on future sales of SPINRAZA.

7. Segment Information and Concentration of Business Risk

We have two reportable segments Ionis Core and Akcea Therapeutics. At December 31, 2018, we owned approximately 75 percent of Akcea. Segment income (loss) from operations includes revenue less operating expenses attributable to each segment.

In our Ionis Core segment we are exploiting our antisense technology to generate a broad pipeline of first-in-class and/or best-in-class medicines for us and our partners. Our Ionis Core segment generates revenue from a multifaceted partnering strategy.

Akcea is a biopharmaceutical company focused on developing and commercializing medicines to treat patients with rare and serious diseases.

The following tables show our segment revenue and income (loss) from operations for 2018, 2017 and 2016 (in thousands), respectively.

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

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

2016 (as revised)	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$ 883	$ —	$ —	$ 883
Licensing and other royalty revenue	21,884	—	—	21,884
Total commercial revenue	22,767	—	—	22,767
R&D revenue under collaborative agreements	362,657	—	(12,648)	350,009
Total segment revenue	$ 385,424	$ —	$ (12,648)	$ 372,776
Total operating expenses	$ 322,192	$ 83,512	$ (12,768)	$ 392,936
Income (loss) from operations	$ 63,232	$ (83,512)	$ 120	$ (20,160)

The following table shows our total assets by segment at December 31, 2018 and 2017 (in thousands), respectively.

Total Assets	Ionis Core	Akcea Therapeutics	Elimination of Intercompany Activity	Total
December 31, 2018	$ 2,975,491	$ 365,261	$ (672,968)	$ 2,667,784
December 31, 2017 (as revised)	$ 1,342,578	$ 268,804	$ (288,608)	$ 1,322,774

Contracts receivables at December 31, 2018 and December 31, 2017 were comprised of approximately 99 percent and 84 percent for each year from four and 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 $18,500 and $24,500 in 2018 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately $5.7 million, $3.0 million and $1.7 million in matching contributions for the years ended December 31, 2018, 2017 and 2016, 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 U.S. District Court of Northern District of California related to U.S. 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. In April 2018, the Court of Appeals issued its ruling affirming the District Court's finding of unenforceability based on unclean hands. Having upheld the ruling that the patents are unenforceable against Gilead, the court did not reach the question of validity. In September 2018, we filed a petition requesting a hearing before the Supreme Court, asserting that it was improper for the trial court to overturn the jury verdict on the basis of the equitable defense of unclean hands. In January 2019, the Supreme Court denied our petition. 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, 2018 and 2017 are as follows (in thousands, except per share data).

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

2017 Quarters (as revised)	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue	$ 115,800	$ 112,273	$ 118,314	$ 167,792
Operating expenses	$ 96,315	$ 105,823	$ 107,002	$ 173,992
Income (loss) from operations	$ 19,485	$ 6,450	$ 11,312	$ (6,200)
Net income (loss)	$ 8,964	$ (3,085)	$ (7,493)	$ (9,169)
Net income (loss) attributable to Ionis Pharmaceutical, Inc. common stockholders	8,964	(3,085)	(2,611)	(2,922)
Basic net income (loss) per share (1) (2)	$ 0.07	$ (0.02)	$ (0.02)	$ (0.03)
Diluted net income (loss) per share (1) (3)	$ 0.07	$ (0.02)	$ (0.02)	$ (0.03)

(1) We computed net income (loss) per share independently for each of the quarters presented. Therefore, the sum of the quarterly net income (loss) per share will not necessarily equal the total for the year.

(2) As discussed in Note 1, *Organization and Significant Accounting Policies,* we compute basic net income (loss) per share by dividing the total net income (loss) attributable to our common stockholders by our weighted-average number of common shares outstanding during the period. Our basic net income (loss) per share calculation for each of the quarters in 2018 and for the third and fourth quarters of 2017 considered our net income for Ionis on a stand-alone basis plus our share of Akcea's net loss for the period. To calculate the portion of Akcea's net loss attributable to our ownership, we multiplied Akcea's loss per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net income (loss) available to Ionis common stockholders for the calculation of net income (loss) per share is different than net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders in the consolidated statements of operations.

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

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

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

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

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

Prior to Akcea's IPO in July 2017, we owned Akcea series A convertible preferred stock, which included a six percent cumulative dividend. Upon completion of Akcea's IPO in July 2017, our preferred stock was converted into common stock on a 1:1 basis. The preferred stock dividend was not paid at the IPO because the IPO was not a liquidation event or a change in control. During 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 that we owned in our calculation of basic and diluted net income (loss) per share for the three months ended September 30, 2017.

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 Loss Per Share	Ionis' Portion of Akcea's Net Loss
Common shares	36,556	$ (0.33)	$ (12,063)
Preferred shares	5,651	(0.01)	(57)
Akcea's net loss attributable to our ownership			$ (12,120)
Ionis' stand-alone net income			10,144
Net loss available to Ionis common stockholders			$ (1,976)
Weighted average shares outstanding			124,370
Basic net loss per share			$ (0.02)

Our basic net income (loss) per share for the three months ended December 30, 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	$ (0.30)	$ (13,634)
Akcea's net loss attributable to our ownership			$ (13,634)
Ionis' stand-alone net income			10,510
Net loss available to Ionis common stockholders			$ (3,124)
Weighted average shares outstanding			124,818
Basic net loss per share			$ (0.03)

(3) For the three months ended December 31, 2018, we had net income available to Ionis common stockholders. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during those periods. Diluted common equivalent shares for the three months ended December 31, 2018 consisted of the following (in thousands except per share amounts):

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

For the three months ended March 31, 2017, we owned 100 percent of Akcea. As a result, we did not have to adjust our earnings per share calculation. 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 those periods. Diluted common equivalent shares for the three months ended March 31, 2017 consisted of the following (in thousands except per share amounts):

Three Months Ended March 31, 2017	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 8,964	122,861	$ 0.07
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 Ionis common stockholders	$ 8,964	124,972	$ 0.07

For the three months ended March 31, 2017, the calculation excluded the 1 percent and 2¾ percent notes because the effect on diluted earnings per share was anti-dilutive.

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(B)(4) AND 240.24B-2

EXHIBIT 10.67

FACTOR B DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

AMONG

IONIS PHARMACEUTICALS, INC.,

AND

F. HOFFMANN-LA ROCHE LTD

AND

HOFFMANN-LA ROCHE INC.

FACTOR B DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

This FACTOR B DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT (the "Agreement") is entered into as of the 9th day of October, 2018 (the "***Effective Date***") by and among **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010 ("***Ionis***"), and **F. HOFFMANN-LA ROCHE LTD**, a Swiss corporation, having its principal place of business at Grenzacherstrasse 124, 4070 Basel, Switzerland ("***Roche Basel***") and **HOFFMANN-LA ROCHE INC.**, a New Jersey corporation, having its principal place of business at 150 Clove Road, Suite 8, Little Falls, New Jersey 07424 ("***Roche US***"; Roche Basel and Roche US are collectively referred to as "***Roche***"). Roche and Ionis each may be referred to herein individually as a "***Party***" or collectively as the "***Parties***".

RECITALS

WHEREAS, Ionis has expertise in discovering and developing antisense drugs, and is developing the antisense drug IONIS-FB-L_{Rx};

WHEREAS, Roche has expertise in developing and commercializing drugs, and Roche is interested in developing and commercializing IONIS-FB-L_{Rx};

WHEREAS, Roche desires Ionis to develop IONIS-FB-L_{Rx} through completion of a phase 2 trial in the ophthalmological indication of geographic atrophy and an anticipated phase 2a trial in [***] and grant Roche an option to obtain an exclusive license to develop and commercialize such drug;

NOW, THEREFORE, in consideration of the respective covenants, representations, warranties and agreements set forth herein, the Parties hereto agree as follows:

ARTICLE 1.
DEFINITIONS

The terms used in this Agreement with initial letters capitalized, whether used in the singular or the plural, will have the meaning set forth in APPENDIX 1, or if not listed in APPENDIX 1, the meaning designated in places throughout the Agreement.

ARTICLE 2.
AGREEMENT OVERVIEW

The intent of the Collaboration is for the Parties to develop IONIS-FB-L_{Rx} for (i) the treatment of geographic atrophy ("***GA***"), and (ii) potentially the treatment of [***] ("***[***]***"). Ionis will Develop IONIS-FB-L_{Rx} through Completion of the Proposed Phase 2 Trials. Roche will have an Option to obtain an exclusive license to further Develop, Manufacture, and Commercialize IONIS-FB-L_{Rx}. Unless terminated earlier, the Option will be exercisable from any time the last patient specified in the most current version of the Development Plan (i.e. the initial Development Plan as modified by the JSC) has been enrolled in the Phase 2 GA Trial until the Option Deadline (the "***Option Period***"). If Roche exercises its Option, Roche will be responsible for all further Development, Manufacturing and Commercializing activities related to the Products, except for any Phase 2 Trials then being conducted by Ionis under the Development Plan. The purpose of this ARTICLE 2 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement with regard to the Development and Commercialization of the Products, and therefore this ARTICLE 2 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

ARTICLE 3.
DEVELOPMENT COLLABORATION FOR IONIS-FB-L_{Rx}

3.1. **Development Activities for IONIS-FB-L_{Rx}.** The Parties will Develop IONIS-FB-L_{Rx} under a development plan agreed between the Parties or as may be amended by the JSC from time to time, which covers all Clinical Studies to be conducted through completion of the Development activities necessary to obtain Approval of a Product in at least one (1) Indication (such plan, the "***Development Plan***", and such program, the "***Development Program***"). Each Party will use Commercially Reasonable Efforts to conduct the Development activities assigned to such Party under, and in accordance with, the Development Plan; *provided that* neither Roche nor Ionis will have any obligation to perform any activity that, after having consulted the JSC or the applicable JDC, it in good faith believes that continuing such activity would violate any Applicable Law, ethical principles, or principles of scientific integrity.

3.1.1. **Development Plan**. As of the Effective Date, the Parties have agreed to an initial Development Plan, which includes a clinical trial protocol synopsis for the Phase 2 GA Trial (the "***GA Protocol***") and a general outline for the Phase 2 [***] Trial. Until the sooner of, the Development Plan is replaced by the IDCP under Section 8.1.1 or the JSC is dissolved, the Development Plan will be updated at least annually by the JSC and the applicable JDC. Subject to Section 4.1.1(b)(ii) below, any changes to the Development Plan must be agreed to by the JSC and the applicable JDC.

3.1.2. **Proposed Phase 2 Trials**.

(a) **Phase 2 GA Trial**. Ionis will conduct the Phase 2 GA Trial under the GA Protocol. Ionis will use Commercially Reasonable Efforts to meet the timeline for the Phase 2 GA Trial as determined by the JSC and the applicable JDC, including to meet the Specific Performance Milestone Events in APPENDIX 2. Ionis will keep Roche informed of the progress of such Phase 2 GA Trial through the JSC and applicable JDC.

(b) **Phase 2 [***] Trial**. Ionis will conduct the Phase 2 [***] Trial under a protocol to be finalized through the JSC and the applicable JDC. Ionis will use Commercially Reasonable Efforts to meet the timeline for the Phase 2 [***] Trial as determined by the JSC and the applicable JDC, including to meet the Specific Performance Milestone Events in APPENDIX 2. Ionis will keep Roche informed of the progress of such Phase 2 [***] through the JSC and applicable JDC.

(c) **Phase 2 Trial Data Package and Interim Data**. Promptly after conducting interim data analysis related to either the Phase 2 GA Trial or the Phase 2 [***] Trial (if any), Ionis will provide to Roche a copy of its analyses and the underlying data sufficient for Roche to conduct a pharmacokinetics and/or pharmacodynamics analysis, and ongoing safety data (which will be provided by Ionis to Roche on an ongoing basis). Once available to Ionis, Ionis will promptly deliver to Roche the Phase 2 Trial Data Package.

3.1.3. **Additional Development of IONIS-FB-L_{Rx}**. The Parties are discussing additional Development (clinical or non-clinical) of IONIS-FB-L_{Rx} and will continue such discussions in good faith prior to Option exercise.

(a) If, before Option exercise, Ionis and Roche agree that Ionis will conduct an additional Phase 2 Trial or any additional earlier stage Clinical Study for the Product, then the Parties will share the costs of such additional Phase 2 Trial and negotiate in good faith the design and reimbursement terms for such Clinical Study(ies), including a budget, payment schedule, an appropriate methodology to allocate the costs of such Clinical Study(ies), and who will supply clinical-grade API and Finished Drug Product, and the JSC and the applicable JDC will revise the Development Plan to include a clinical trial protocol synopsis for each such Clinical Study.

(b) If, before Option exercise, Ionis (but not Roche) would like to conduct a phase 2b trial in [***] (the "***Phase 2b [***] Trial***"), then [***] such Phase 2b [***] Trial, and upon Initiation of a Registration-Directed Trial for [***] after Option exercise, Roche will pay to Ionis [***] within [***] days after Initiation of a Registration-Directed Trial for [***] and Roche's receipt of an invoice from Ionis. Initiation of the Registration-Directed Trial for [***] is at the sole discretion of Roche. For clarity, no such payment will be required if Roche does not provide the Option Exercise Notification. For clarity, the payment in this clause (b) is not applicable to clauses (a) or (c).

(c) If Roche would like Ionis to conduct the Phase 2b [***] Trial but Ionis is unable or unwilling to conduct such trial, then Roche may undertake such Phase 2b [***] under Ionis' IND and Roche will pay [***] but may offset [***] of Roche's reasonable costs incurred in running the Phase 2b [***] Trial before Option exercise against the next Post-Licensing Milestone Payment under TABLE 1 of Section 9.4 that becomes due. Ionis will use Commercially Reasonable Efforts to comply with Roche's reasonable requests for support regarding Regulatory Materials and interactions with Regulatory Authorities and other activities required to conduct the Phase 2b [***] Trial under the Ionis IND.

3.1.4. **Attaching Plans to JSC Minutes**. The JSC will attach each revised Development Plan to the meeting minutes of the JSC.

3.1.5. **Development Plan Costs**. Before Option exercise, except as the Parties may otherwise agree, Ionis will be responsible for all costs and expenses associated with the activities assigned to Ionis under the Development Plan, and Roche will be responsible for all costs and expenses associated with the activities assigned to Roche under the Development Plan. Before Option exercise, if the Parties mutually agree to a material change to the Development Program (e.g., add a new arm or increase the maximum number of study subjects) or a Regulatory Authority requires Ionis to change the Development Program (each an "***Approved Change***"), the Parties will share the Approved Change Costs (as defined below) as follows:

(a) If the Approved Change Costs are less than [***], then [***] will be responsible for the Approved Change Costs.

(b) If the Approved Change Costs are [***]or higher and less than [***], then [***] will be responsible for the Approved Change Costs for the first [***] and [***] will be responsible for the Approved Change Costs above [***].

(c) If the Approved Change Costs are [***] or more, then each Party will be responsible for one half of the portion of the Approved Change Costs. Each Party may credit any amounts paid under Section 3.1.5(a) and Section 3.1.5(b) against amounts payable under this Section 3.1.5(c).

For clarity, the allocation of Approved Change Costs set forth in this Section 3.1.5 will not apply to cost overruns associated with the Development Program that are not caused by Approved Changes. For example, activities to improve recruitment rate (e.g., adding additional sites (other than due to the addition of a new arm or due to an increase in the maximum number of study subjects, or the addition of sites such that the total number of sites exceeds [***]) or increasing site payments), recruitment vendors, or costs resulting from a delay in study conduct, are cost overruns associated with the Development Program and are not Approved Changes.

"***Approved Change Costs***" means [***] in each case with regard to clause (2) without considering the aggregate effect of all Approved Changes.

3.1.6. **Development Term**. The term for the conduct of the Development Program under the Development Plan will begin on the date work began under such Development Plan and will end upon the earlier of (i) completion of all Development activities under such Development Plan to support Approval in at least one (1) Indication in all Major Markets, (ii) the termination of such Development Program in accordance with Section 13.2.1, and (iii) mutual agreement of the Parties to terminate the Development Program.

3.2. **Regulatory Matters**. Before Option exercise and until Completion of the Proposed Phase 2 Trials, Ionis will be responsible for all communications with Regulatory Authorities regarding a Product and will have final decision-making authority with respect to the matters set forth in this Section 3.2.

3.2.1. **Participation in Regulatory Meetings**. Ionis will provide Roche with as much advance written notice as practicable of any meetings that Ionis has or plans to have with a Regulatory Authority regarding the Proposed Phase 2 Trials and any other Phase 2 Trial or earlier stage Clinical Study that the Parties agree Ionis will conduct for a Product and will allow Roche (at Roche's own expense) to participate in any such meetings as an observer.

3.2.2. **Regulatory Communications**. Ionis will provide Roche with copies of documents and communications submitted to and received from Regulatory Authorities that materially impact the Development or Commercialization of a Product for Roche's review and comment, and Ionis will consider in good faith including any comments provided by Roche to such documents and communications.

ARTICLE 4.
COLLABORATION GOVERNANCE; MANUFACTURING AND COSTS

4.1. **Collaboration Governance**.

4.1.1. **Joint Steering Committee**. Within thirty (30) days after the Effective Date, the Parties will establish a joint steering committee ("***JSC***") to govern the activities under the Development Plan. The JSC will consist of three (3) representatives appointed by Ionis and three (3) representatives appointed by Roche. Each Party's JSC representatives will be senior personnel empowered by such Party to make decisions related to clinical development and regulatory strategy, and at least one of each Party's members will have operational responsibility for such Party's respective activities under the Development Plan. Each Party will be responsible for the costs and expenses of its own employees or consultants attending JSC meetings. The JSC will meet at least twice each Calendar Year but not more that four (4) times per Calendar Year. Ionis will have the right, but not the obligation, to participate in the JSC after Option exercise. If Ionis chooses not to participate, then Roche can dissolve the JSC.

(a) **Role of the JSC**. Without limiting any of the foregoing, subject to Section 4.1.1(b), 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 updates to the Development Plan with respect to the Proposed Phase 2 Trials as well as with respect to any Phase 2 Trial undertaken per Section 3.1.3 (including any material changes) as contemplated under Section 3.1;

(ii) Review and approve regulatory filings regarding the Clinical Studies under the Development Plan with respect to the Proposed Phase 2 Trials as well as with respect to any Phase 2 Trial undertaken per Section 3.1.3 in accordance with Section 3.2;

(iii) Oversee the operation of any JDC regarding the Clinical Studies under the Development Plan with respect to the Proposed Phase 2 Trials as well as with respect to any Phase 2 Trial undertaken per Section 3.1.3;

(iv) Attempt to informally resolve any disputes that may arise between the Parties regarding the Proposed Phase 2 Trials as well as any Phase 2 Trial undertaken per Section 3.1.3; and

(v) Such other review, approval and advisory responsibilities as may be assigned to the JSC by the Parties pursuant to this Agreement.

(b) **Decision Making**.

(i) **Committee Decision Making**. Decisions by the JSC will be made by unanimous consent with each Party's representatives having, collectively, one vote. At any given meeting of the JSC, a quorum will be deemed reached if a voting representative of each Party is present or participating in such meeting. No action taken at any meeting of the JSC 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.

(ii) **Implementation**. Each Party will give due consideration to, and consider in good faith, the recommendations and advice of the JSC regarding the conduct of the activities under the Development Plan. The JSC will endeavor in good faith to reach consensus on all decisions, *however*, if the JSC cannot unanimously agree on a matter to be decided by it within fifteen (15) Business Days, then the matter may be referred to the Executives for resolution as set forth in Section 15.1.1. If the Executives cannot reach agreement, then (i) before Option exercise, Ionis will have the final decision-making authority regarding the performance of activities under the Development Plan and whether to accept and how to implement the JSC's recommendations with respect thereto, and (ii) after Option exercise, Roche will have the final decision-making authority regarding the performance of activities under the Development Plan and whether to accept and how to implement the JSC's recommendations with respect thereto, except with respect to decisions regarding operational aspects of a Phase 2 Trial conducted by Ionis that has not yet Completed, which will be within Ionis' final decision-making authority. In exercising its final decision-making authority under this Section 4.1.1(b)(ii), a Party will not increase the other Party's costs or obligations under the Development Plan without such Party's 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.

4.1.2. **Joint Development Committees**. Prior to the Initiation of the Phase 2 GA Trial and the Phase 2 [***] Trial, as applicable, the Parties will establish a joint development committee ("***JDC***") for the Phase 2 GA Trial and a separate JDC for the Phase 2 [***] Trial. Thereafter, if the Parties agree that Ionis will conduct any other Phase 2 Trial under the Development Plan, within thirty (30) days after such agreement, the Parties will establish a separate JDC for such Phase 2 Trial. Each JDC will consist of an equal number of representatives appointed by Ionis and Roche. Each Party will be responsible for the costs and expenses of its own employees or consultants attending JDC meetings. Ionis will have the right, but not the obligation, to participate in each JDC after Option exercise. If Ionis chooses not to participate, then Roche can dissolve the JDC. Each JDC will be dissolved as soon as reasonably possible after the Completion of the applicable ongoing Phase 2 Trial over which such JDC has oversight.

(a) **Role of the JDCs**. Without limiting any of the foregoing, subject to Section 4.1.2(b), the applicable JDC will perform the following functions, some or all of which may be addressed directly at any given JDC meeting:

(i) oversee the Parties' activities regarding the applicable Phase 2 Trial under the Development Plan;

(ii) oversee the formation and operation of any subcommittee of the JDC regarding the applicable Phase 2 Trial under the Development Plan;

(iii) with respect to the JDC for the Phase 2 [***] Trial (or the JDC for any subsequent Phase 2 Trial that the Parties agree Ionis will conduct), discuss and agree upon the proposed design and protocol(s) for the Phase 2 [***] Trial (or other Phase 2 Trial, if applicable) under the Development Plan and present such documents to the JSC for final approval; and

(iv) such other review and advisory responsibilities as may be assigned to the applicable JDC by the Parties pursuant to this Agreement.

(b) **Decision Making**. Decisions by the applicable JDC will be made by unanimous consent with each Party's representatives having, collectively, one vote. At any given meeting of the applicable JDC, a quorum will be deemed reached if a voting representative of each Party is present or participating in such meeting. No action taken at any meeting of the applicable JDC 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 applicable JDC has not reached unanimous consensus. Each JDC will endeavor in good faith to reach consensus on all decisions over which it has oversight, *however*, if a JDC cannot unanimously agree on a matter to be decided by it within fifteen (15) Business Days, then the matter will be referred to the JSC for resolution in accordance with Section 4.1.1(b).

4.2. **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 each JDC, and performing the activities listed in SCHEDULE 4.2.

4.3. **Records and Quality; Inspections; Materials Transfer**.

4.3.1. **Records**. Each Party will maintain records consistent with its own practice of all Development and Commercial activities such Party performs under this Agreement and all results, data, inventions and developments made in the performance of such work. Such records will be in sufficient detail and in good scientific manner appropriate for compliance reporting, effective auditing, patent and regulatory purposes. Upon prior written notice, a Party will provide the other Party with copies of all requested records, to the extent reasonably required for the performance of a Party's rights and obligations under this Agreement.

4.3.2. **Materials Transfer**. To facilitate the activities under this Agreement, either Party may provide to the other Party certain materials for use by the other Party in furtherance of the activities to be performed under this Agreement. Unless agreed otherwise between the Parties, all such materials will be used by the receiving Party in accordance with the terms and conditions of this Agreement solely for purposes of exercising its rights and performing its obligations under this Agreement, and the receiving Party will not transfer such materials to any Third Party unless expressly contemplated by this Agreement or upon the written consent of the supplying Party. Except as expressly set forth herein, SUCH MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

4.4. **Manufacturing and Supply**. Unless otherwise expressly agreed by the JSC:

4.4.1. **Supplies for Activities Before Option Exercise**. Ionis is solely responsible for the manufacture and supply of API and Finished Drug Product to support the activities under the Development Plan through Completion of the Proposed Phase 2 Trials, including any costs associated with such manufacture and supply.

4.4.2. **Supplies for Activities After Option Exercise**. After Option exercise, Ionis will deliver to Roche, if Roche desires, any inventory of cGMP and non-cGMP API, cGMP and non-cGMP Finished Drug Product, and cGMP and non-cGMP packaged clinical trial material containing IONIS-FB-L_{Rx} in Ionis' possession and that is not necessary to complete any then ongoing Phase 2 Trials being conducted by Ionis under the Development Plan [***] as set forth in SCHEDULE 4.4.2. After Option exercise, Roche is responsible for the manufacture and supply of API and Finished Drug Product to support the activities under the Development Plan (except for any then-ongoing additional Phase 2 Trial being conducted by Ionis and any then-ongoing Proposed Phase 2 Trials) and to Commercialize Product, including any costs associated with such manufacture and supply, and Ionis will, at Roche's election either (i) assign to Roche contracts Ionis has with Third Party manufacturers for the manufacture of such API or Finished Drug Product and will use commercially reasonable efforts to support Roche in qualifying such Third Party manufacturers, or (ii) transfer to Roche the Ionis Manufacturing and Analytical Know-How in accordance with Section 7.2.2, subject to Section 7.2.3. If, prior to Option exercise, Roche elects to perform preliminary chemistry, manufacturing and controls work to evaluate the feasibility of manufacturing the Product or to determine whether to pursue either of the foregoing options specified in this Section 4.4.2, Ionis will cooperate in good faith with Roche and will provide the materials and information requested by Roche necessary to such evaluation. Each Party shall bear its own costs for such activities pursuant to the preceeding sentence.

4.5. **Subcontracting**. Each Party may engage Third Party subcontractors to perform certain of its obligations under this Agreement. Any subcontractor engaged to perform a Party's obligations under this Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity and will execute such Party's standard nondisclosure agreement. Any Party engaging a subcontractor hereunder will remain responsible for such activities.

4.6. **Applicable Laws**. Each Party will perform its activities pursuant to this Agreement in compliance with Applicable Law, including good laboratory and clinical practices and cGMP, in each case as applicable in the country, state, province, territory, and locale wherein such activities are conducted.

ARTICLE 5.
EXCLUSIVITY COVENANTS

5.1. **Exclusivity Covenants**. 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 5.1.3:

5.1.1. **Before Option Exercise**. Before Option exercise, Ionis will work exclusively within the collaboration described in the Agreement to conduct all discovery, research, development, manufacture or commercialization of an ASO that is designed to bind to the RNA that encodes Factor B in the Field.

5.1.2. **After Option Exercise**.

(a) After Option exercise, if Roche is Developing or Commercializing at least one Product under this Agreement, neither Ionis nor Roche independently or for or with any of their respective Affiliates or any Third Party (including the grant of any license to any Third Party) will sell an ASO approved by a Regulatory Authority for marketing and sale that is designed to bind to the RNA that encodes Factor B in the Field until the Full Royalty Period ends in the first Major Market. After the end of the Full Royalty Period in the first Major Market, the exclusivity covenants set forth in this Section 5.1.2(a) will continue on a country-by-country basis in each country where the Full Royalty Period still applies [***].

(b) The exclusivity covenants of Section 5.1.2(a) will not apply to [***] or [***], *provided that* Roche [***], or otherwise [***].

5.1.3. **Limitations and Exceptions to Ionis' and Roche's Exclusivity Covenants**. Notwithstanding anything to the contrary in Section 5.1, the Parties and their Affiliates may perform the following activities:

(a) all activities permitted or contemplated under this Agreement; and

(b) with regard to Ionis and its Affiliates:

(i) any activities pursuant to the Prior Agreement;

(ii) the granting of, or performance of obligations under, Permitted Licenses.

5.2. **Effect of Exclusivity on Indications**. Ionis and Roche are subject to certain exclusivity covenants under Section 5.1; *however*, the Parties acknowledge and agree that each Party (on its own or with a Third Party, or an Affiliate) may pursue products for the same Indication as a Product so long as such product is not an ASO designed to bind to the RNA that encodes Factor B.

ARTICLE 6.
EXCLUSIVE OPTION

6.1. **Option and Option Deadline**. Ionis hereby grants Roche an exclusive option to obtain the license set forth in Section 7.1.1 (the "***Option***"). To obtain the license set forth in Section 7.1.1, Roche must exercise the Option by the [***] following Roche's receipt of the Phase 2 Trial Data Package from Ionis (the "***Option Deadline***"). If, however, the Phase 2 GA Trial [***] and Roche is conducting the Phase 2b [***] Trial under Section 3.1.3(c) or Ionis is conducting an additional Phase 2 Trial or any additional earlier stage Clinical Study for the Product under Section 3.1.3(a), then the Option Deadline will be extended until [***] after the Completion of the Phase 2b [***] Trial.

6.2. **Option Exercise; Option Expiration**. During the Option Period, if, by the Option Deadline, Roche (i) notifies Ionis in writing that it is exercising the Option ("***Option Exercise Notification***"), and (ii) within [***] after the latest of (x) the Option Exercise Notification, (y) Roche's receipt of an invoice from Ionis, and (z) expiration or termination of any applicable waiting period under the HSR Act or any other similar Applicable Law, Roche timely pays Ionis the license fee set forth in Section 9.3, Ionis will, and hereby does, grant Roche the license set forth in Section 7.1.1. Prior to the Option Deadline, Roche will have the full opportunity to conduct due diligence to evaluate whether to exercise the Option and Ionis will cooperate with Roche and ensure that all necessary data and information, including clinical and manufacturing data and any available [***] analysis, are provided to Roche. If, by the Option Deadline, Roche has not provided Ionis the Option Exercise Notification, and within [***] after the latest of (1) providing the Option Exercise Notification, (2) receiving an invoice from Ionis for the license fee set forth in Section 9.3, and (3) expiration or termination of any applicable waiting period under the HSR Act or any other similar Applicable Law, has not paid Ionis the license fee set forth in Section 9.3, then Roche's Option will expire. If Roche's Option expires, then Section 13.4.1 and Section 13.4.2 will apply.

6.3. **HSR**. Each Party will (i) cooperate with the other Party in the preparation, execution and filing of all documents that may be required pursuant to the HSR Act or any other Applicable Law, and (ii) observe all applicable waiting periods before consummating the Option exercise as set forth in Section 6.2. Each Party will bear its own costs (including counsel or other expert fees) with respect to preparing, executing and filing such documents. Subject to the terms and conditions of this Agreement, each Party will use all reasonable efforts to take, or cause to be taken, all reasonable actions and to do, or cause to be done, all things necessary and appropriate to consummate the exercise of the Option contemplated by Section 6.2 of this Agreement, should Roche choose to exercise the Option. Notwithstanding anything to the contrary contained in this Agreement, Roche will have the sole and exclusive right to determine, at its discretion but without any obligation whatsoever, whether it will have any obligation to take any actions in connection with, or agree to, any demands for the license, sale divestiture or disposition of assets of Roche or its Affiliates or Ionis, asserted by the United States Federal Trade Commission, the Antitrust Division of the United States Department of Justice or any other Regulatory Authority in connection with antitrust matters or international competition laws, or to defend through litigation any proceeding commenced by the Federal Trade Commission, the Antitrust Division of the United States Department of Justice or other governmental authority in connection with the foregoing matters.

ARTICLE 7.
LICENSE GRANTS

7.1. License Grants; Sublicense Rights.

7.1.1. Development and Commercialization License Grant to Roche. Subject to the terms of this Agreement, effective upon Roche's exercise of the Option in accordance with this Agreement, Ionis grants to Roche a worldwide, exclusive, royalty-bearing, sublicensable (in accordance with Section 7.1.4 below) license under the Licensed Intellectual Property to Develop, Manufacture, have Manufactured (in accordance with Section 7.1.4 below), use, and Commercialize Products in the Field.

7.1.2. Cross Licenses under Collaboration Intellectual Property.

(a) Enabling Patent License from Roche to Ionis. Subject to the terms and conditions of this Agreement (including Ionis' exclusivity covenants under Section 5.1 and without limiting the license granted to Roche under Section 7.1.1), Roche hereby grants Ionis a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicensable license under any Roche Collaboration Intellectual Property (excluding any Product-Specific Patents) to research, develop, manufacture, have manufactured and commercialize products that include an ASO as an active pharmaceutical ingredient (other than a Product that is being Developed or Commercialized by Roche, its Affiliates or Sublicensees under this Agreement or the HTT Research, Development, Option and License Agreement among the Parties dated April 8, 2013).

(b) Enabling Patent License from Ionis to Roche. Subject to the terms and conditions of this Agreement (including Roche's exclusivity covenants under Section 5.1 and without limiting the license granted to Roche under Section 7.1.1), Ionis hereby grants Roche a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicensable license under any Ionis Collaboration Intellectual Property (excluding any Ionis Product-Specific Patents) to research, develop, manufacture, have manufactured and commercialize products that do not include an ASO as an active pharmaceutical ingredient.

7.1.3. Amendment to the Existing Diagnostic Agreement. After Option exercise, Ionis and Roche will execute an amendment to the Existing Diagnostic Agreement on terms mutually agreed by Roche and Ionis, which amendment will include granting Roche a non-exclusive, sublicensable, worldwide license, with the right to sublicense (through multiple tiers) under Patent Rights and/or Know-How Controlled by Ionis necessary or useful to research, develop , manufacture, have manufactured, and commercialize Factor B diagnostic products (including diagnostic products and/or services to select patients who will use Products).

7.1.4. Sublicense Rights.

(a) Subject to the terms of this Agreement, Roche will have the right to grant sublicenses under any license granted under Section 7.1.1 above:

(i) under Ionis' interest in Jointly Owned Collaboration IP to the extent it is exclusively licensed to Roche under this Agreement, the Ionis Core Technology Patents, Ionis Product-Specific Patents, Ionis Collaboration Patents, Ionis Collaboration Know-How, and Ionis Know-How to an Affiliate of Roche or a Third Party; and

(ii) under the Ionis Manufacturing and Analytical Patents and Ionis Manufacturing and Analytical Know-How solely to (y) an Affiliate of Roche or (z) a [***] (each, a "***Licensed CMO***").

(b) **Requests to Grant Sublicenses to CMOs**. If Roche provides Ionis with a written request that Ionis grant a license under the Ionis Manufacturing and Analytical Patents and Ionis Manufacturing and Analytical Know-How to a CMO designated by Roche that is not a Licensed CMO, solely for such CMO to manufacture Products for Roche, its Affiliate or Sublicensee in a manufacturing facility owned or operated by such CMO, [***].

(c) **Enforcing Sublicenses**. Each sublicense by Roche under this Agreement will be subject to, and consistent with, the terms of this Agreement. Roche will be responsible to ensure compliance by its Sublicensees with the terms and conditions of this Agreement. If Ionis reasonably believes a Roche Sublicensee may be violating the terms of this Agreement, then, within thirty (30) days after Ionis delivers a written request to Roche, Roche will provide Ionis a full and complete copy of the sublicense Roche entered with such Sublicensee.

(d) **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, any Sublicensee granted a sublicense by Roche to Develop or Commercialize Products 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 Roche; *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 Roche, 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 Roche. Roche 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.

7.1.5. **No Implied Licenses**. All rights in and to Licensed Intellectual Property not expressly licensed to Roche under this Agreement are hereby retained by Ionis or its Affiliates. All rights in and to Roche Intellectual Property not expressly licensed or assigned to Ionis under this Agreement, are hereby retained by Roche 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.

7.1.6. **License Conditions; Limitations**. Subject to Section 9.10, any license granted under Section 7.1.1 and the sublicense rights under Section 7.1.4 is subject to and limited by (i) the Permitted Licenses, (ii) the Prior Agreement, and (iii), if any, the Additional Ionis In-License Agreements, in each case to the extent the provisions of such obligations or agreements are specifically disclosed to Roche in writing (or via electronic data room).

7.1.7. **Trademarks for Products**. After Option exercise, Roche is solely responsible for all trademarks, trade dress, logos, slogans, designs, copyrights and domain names used on or in connection with Products licensed under Section 7.1.1.

7.2. **Technology Transfer after Option Exercise**. After Option exercise pursuant to a technology transfer plan to be mutually agreed by Ionis and Roche, and subject to Section 7.2.3, Ionis will:

7.2.1. **Licensed Know-How – Generally**. Deliver to Roche copies of Licensed Know-How (other than the Ionis Manufacturing and Analytical Know-How) in the Field in Ionis' possession not previously provided hereunder, for use solely in accordance with the license granted under Section 7.1.1 to Roche, together with all regulatory documentation (including drafts) related to any Phase 2 Trial Completed as of Option exercise. Following Option exercise, the Parties will promptly agree on a plan to transfer to Roche (i) all regulatory documentation (including drafts) related to any Phase 2 Trial in progress as of Option exercise following the Completion of such Phase 2 Trial and (ii) any other regulatory documentation regarding the Product in Ionis' possession not previously provided to Roche. To assist with the transfer of such Licensed Know-How, Ionis will make its personnel reasonably available to Roche during normal business hours to transfer such Licensed Know-How under this Section 7.2.1.

7.2.2. **Ionis Manufacturing and Analytical Know-How**. Deliver, at Roche's election, to one of either (i) Roche or (ii) a Licensed CMO solely to Manufacture API and Finished Drug Product on Roche's behalf, copies of the Ionis Manufacturing and Analytical Know-How relating to Products in Ionis' possession not previously provided hereunder, which is necessary for the exercise by Roche, its Affiliates or a Third Party of the Manufacturing rights granted under Section 7.1.1.

7.2.3. **Technology Transfer Costs**. Perform the technology transfer activities under this Section 7.2 for up to [***] FTE hours (free of charge to Roche) of Ionis' time. Thereafter, if requested by Roche, Ionis will provide Roche with a reasonable level of assistance in connection with such transfer, which Roche will reimburse Ionis for Ionis' time incurred in providing such assistance at Ionis' then-current FTE rate, and any of Ionis' reasonable travel expenses for travel requested by Roche, and any outside consultants' costs and consultants' reasonable travel expenses incurred by Ionis agreed in advance by Roche.

ARTICLE 8.
DEVELOPMENT, MANUFACTURING AND COMMERCIALIZATION

8.1. **Roche Diligence**. After Option exercise, subject to the terms of this Agreement, Roche is 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 the Products, except with respect to any Phase 2 Trial being conducted by Ionis under the Development Plan that has not yet Completed by the time of Option exercise, which will remain the responsibility of Ionis until such Phase 2 Trial has Completed. Roche will use Commercially Reasonable Efforts to Develop, Manufacture and Commercialize Products, including to meet the timelines and milestones set forth in the Development Plan, the IDCP and the Specific Performance Milestone Events.

8.1.1. **Replacement of Development Plan with the IDCP**. Prior to Initiation of the first Registration-Directed Trial for a given Product, Roche will prepare a global integrated development and commercialization plan ("***IDCP***") outlining key aspects for Developing such Product through Approval of at least one (1) Indication, and Roche's worldwide strategy to launch and Commercialize such Product. The IDCP will incorporate and replace the Development Plan and will take the form of, and contain information consistent with, Roche's Development and Commercialization plans for its similar products at similar stages of development or commercialization, including Product Sales forecasts. Once Roche has prepared such plan, Roche will update the IDCP consistent with Roche's standard practice and provide such updates to Ionis at least Annually.

8.1.2. **Registration-Directed Trials**. The Registration-Directed Trials will be designed in accordance with the Registration-Directed Trial designs set forth in the applicable IDCP. Roche will keep Ionis informed of the progress and status of each Registration-Directed Trial. Roche will notify Ionis in writing promptly after Roche completes each Registration-Directed Trial under the applicable IDCP. Once the data generated under the statistical analysis plan for a Registration-Directed Trial is available to Roche, Roche will provide promptly such data to Ionis.

8.1.3. **Investigator's Brochure**. After Option exercise, in addition to the IDCP, Roche will keep Ionis reasonably informed with respect to the status, activities and progress of Development of Products by providing updated versions of the investigator's brochure to Ionis Annually and upon any substantive change to the safety or risk of the Products.

8.1.4. **Participation in Regulatory Meetings**. Each Party will provide the other Party with as much advance written notice as practicable of any meetings such Party has or plans to have with a Regulatory Authority regarding pre-approval or Approval matters for a Product and will allow the other Party (at such other Party's own expense) to participate in any such meetings as an observer. After Option exercise and upon transfer of the IND for IONIS-FB-L_{Rx} to Roche, Roche will lead all interactions with Regulatory Authorities regarding IONIS-FB-L_{Rx} and Products.

8.1.5. **Regulatory Communications**. Each Party will provide the other Party with copies of documents and communications submitted to and received from Regulatory Authorities that materially impact the Development or Commercialization of Products for the other Party's review and comment, and the submitting Party will consider in good faith including any comments provided by the reviewing Party to such documents and communications.

8.1.6. **Participation in Roche Clinical Development Team Meetings**. [***], Roche will permit Ionis to participate in Roche's key clinical development team meetings for Products (*i.e.*, meetings that are likely to have a material impact on the Development of the Product(s) (each such meeting, a "***Key Meeting***"), at Ionis' reasonable request. Ionis' and Roche's respective designated clinical leaders will work together to come up with a schedule of such Key Meetings, giving Ionis as much advance written notice as practicable so that Ionis may, at Ionis' expense, plan for its participation in such meetings.

8.1.7. **Class Generic Claims**. If Roche intends to make any claims in a Product label or regulatory filing that are class generic to ASOs or Ionis' chemistry platform(s), Roche will provide such claims and regulatory filings to Ionis in advance and will consider in good faith any proposals and comments made by Ionis.

8.2. **IND; Global Safety Database**.

8.2.1. **Transfer of the IONIS-FB-L_{Rx} IND to Roche; Global Safety Database Responsibilities.** Until the Completion of the Proposed Phase 2 Trials and any other Phase 2 Trial conducted by Ionis under the Development Plan, Ionis will be the holder of the IND for IONIS-FB-L_{Rx}. After Option exercise and upon Completion of the Proposed Phase 2 Trials and any other Phase 2 Trial conducted by Ionis under the Development Plan, Ionis will transfer promptly the IND to Roche. Upon transfer of the IND to Roche and assumption by Roche of regulatory responsibilities under the IND, Roche will assume responsibility for the global safety database related to IONIS-FB-L_{Rx} and Roche will be solely responsible for reporting to Regulatory Authorities in accordance with the Applicable Law for expeditable adverse events and for periodic safety reporting relating to the safety of IONIS-FB-L_{Rx} and will furnish copies of such reports to Ionis.

8.2.2. 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 non-clinical and clinical development and commercialization (the "***Ionis Internal ASO Safety Database***"). The Ionis Internal ASO Safety Database is an internal database owned and maintained by Ionis to maximize Ionis' and its partners' understanding of Ionis' compounds, and it is separate from, and not a substitute for, the global safety database for which Roche will be responsible under Section 8.2.1 above. To maximize understanding of the safety profile and pharmacokinetics of Ionis compounds, after Option exercise, Roche will cooperate in connection with populating the Ionis Internal ASO Safety Database. To the extent collected by Roche and in the form in which Roche uses/stores such information for its own purposes, Roche will make available to Ionis 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 Roche (but Roche will make such information available to Ionis starting no later than thirty (30) days after Roche's receipt of such information). In connection with any reported serious adverse event for a Product, Roche will provide Ionis all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to Products, Roche will make available to Ionis copies of Annual safety updates filed with each IND and the safety sections of any final Clinical Study reports within thirty (30) days following the date such information is filed or is available to Roche, as applicable. Furthermore, Roche will promptly make available to Ionis any supporting data and answer any follow-up questions reasonably requested by Ionis. All such information disclosed by Roche to Ionis will be Roche Confidential Information; *provided, however*, that Ionis may disclose any such Roche Confidential Information to (i) Ionis' other partners pursuant to Section 8.2.2(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 Roche. Roche will contact Ionis' Chief Medical Officer at Ionis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010 (or at such other address/contact designated in writing by Ionis) for matters related to the Ionis Internal ASO Safety Database. Roche will also cause its Affiliates and Sublicensees to comply with this Section 8.2.2(a).

(b) 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 inform Roche of such issues and, if requested, provide the data supporting Ionis' conclusions.

ARTICLE 9.
FINANCIAL PROVISIONS

9.1. **Option Fee**. In partial consideration for Roche's Option hereunder, within ten (10) days following the Effective Date and receipt by Roche of an invoice from Ionis, Roche will pay Ionis an option fee of seventy-five million dollars (US$75,000,000).

9.2. **Pre-Option Development Milestone**. In partial consideration for Roche's Option hereunder, Roche will pay Ionis a pre-option development milestone of [***] (the "***Pre-Option Development Milestone Payment***"), which will be payable within [***] days after Roche receives from Ionis written notice that [***] (the "***Pre-Option Development Milestone Event***") and receipt by Roche of an invoice in such amount from Ionis.

9.3. **License Fee**. Pursuant to Section 6.2, subsequent to Roche's Option Exercise Notification, Roche will pay to Ionis a license fee of [***] within the timelines set forth in Section 6.2.

9.4. **Milestone Payments for Achievement of Post-Licensing Milestone Events**. As further consideration for the licenses granted herein, Roche will pay to Ionis the applicable one-time milestone payments set forth in TABLE 1 below (each, a "***Post-Licensing Milestone Payment***") when the corresponding milestone event listed in TABLE 1 (each, a "***Post-Licensing Milestone Event***") is first achieved by a Product for the specified Indication:

TABLE 1

Post-Licensing Milestone Event	**Post-Licensing Milestone Payment – Non-Rare Disease Indication**	**Post-Licensing Milestone Payment – Second Indication**
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
Total Post-Licensing Milestone Payments	**[***]**	**[***]**

9.5. **Milestone Payments for First Achievement of Sales Milestone Event**. Roche will pay Ionis the applicable one-time milestone payments set forth in TABLE 2 below (each, a "***Sales Milestone Payment***") after the first achievement of the corresponding event listed in TABLE 2 (each, a "***Sales Milestone Event***"), by or on behalf of Roche or its Affiliates or Sublicensees.

TABLE 2

Sales Milestone Event	Sales Milestone Payment
[***] in worldwide Annual Net Sales of a Product	[***]
[***] in worldwide Annual Net Sales of a Product	[***]
[***] in worldwide Annual Net Sales of a Product	[***]
Total Sales Milestone Payments	**[***]**

9.6. **Limitations on Milestone Payments; Exceptions; Notice**.

9.6.1. Each milestone payment set forth in TABLE 1 and TABLE 2 above will be paid only once upon the first achievement of the applicable Milestone Event, regardless of the number of Products subsequently achieving such Milestone Event or the number of times a given Product reaches such Milestone Event.

9.6.2. If a particular Post-Licensing Milestone Event is not achieved because regulatory activities transpired such that achievement of such earlier Post-Licensing Milestone Event was unnecessary or did not otherwise occur, then upon achievement of a later Post-Licensing Milestone Event the Post-Licensing Milestone Payment applicable to such earlier Post-Licensing Milestone Event will also be due. For example, if Roche proceeds directly to [***] without achieving the [***], then upon achieving the [***] Milestone Event, both the [***] and [***] Post-Licensing Milestone Payments will be due. For clarity, [***] or [***] in one region does not trigger milestone payments in other regions.

9.6.3. If a particular Milestone Event is achieved contemporaneously with or in connection with another Milestone Event, then both Milestone Events will be deemed achieved and the milestone payments for both Milestone Events will be due.

9.6.4. Each time a Milestone Event is achieved under Section 9.4 or Section 9.5, Roche will send to Ionis a written notice thereof promptly (but no later than ten (10) Business Days) following the date of achievement of such Milestone Event and such payment will be due within thirty (30) days after the date such Milestone Event was achieved and receipt of an invoice by Roche from Ionis.

9.7. Royalty Payments to Ionis.

9.7.1. Roche Full Royalty. As partial consideration for the rights granted to Roche hereunder, subject to the provisions of this Section 9.7.1 and Section 9.7.2, Roche will pay to Ionis royalties on worldwide Annual Net Sales of Products sold by Roche, its Affiliates or Sublicensees, on a country-by-country and Product-by-Product basis, in each case in the amounts as follows in TABLE 3 below (the "***Roche Full Royalty***"):

TABLE 3		
Royalty Tier	**Worldwide Annual Net Sales of Products**	**Royalty Rate**
1	For the portion of worldwide Annual Net Sales < US$[***]	[***]%
2	For the portion of worldwide Annual Net Sales ≥ US$[***] but < US$[***]	[***]%
3	For the portion of worldwide Annual Net Sales ≥ US$[***] but < US$[***]	[***]%
4	For the portion of worldwide Annual Net Sales ≥ US$[***]	[***]%

(a) For purposes of TABLE 3, Worldwide Annual Net Sales for a particular Product will be calculated by [***].

(b) Roche will pay Ionis royalties on Net Sales of Products arising from named patient and other similar programs under Applicable Laws, and Roche will provide reports and payments to Ionis consistent with Section 9.11. 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 determining the Full Royalty Period.

9.7.2. Application of Royalty Rates. All royalties set forth under Section 9.7.1 are subject to the provisions of this Section 9.7.2, and are payable as follows:

(a) **Full Royalty Period**. Roche's obligation to pay Ionis the Roche 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 latest of (i) the date of expiration of the last Valid Claim within the Licensed Patents Covering such Product in the country in which such Product is used or sold, (ii) the date of expiration of the data exclusivity period conferred by the applicable Regulatory Authority in such country with respect to such Product (e.g., such as in the case of an orphan drug), or (iii) the [***] anniversary of the First Commercial Sale of such Product in such country *unless* a [***] in such country, at which time in lieu of paying the Roche Full Royalty, Roche will pay Ionis the Roche Reduced Royalty for such Product in such country in accordance with Section 9.7.2(b) (such royalty period, the "Full Royalty Period"). For clarity, (X) Licensed Patents that are Jointly-Owned Collaboration Patents, and (Y) Roche Collaboration Patents, 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 Jointly-Owned Collaboration Patent or Roche Collaboration Patent.

(b) **Reduced Royalty Period**. Subject to Section 9.7.2(c), on a country-by-country and Product-by-Product basis, after the expiration of the Full Royalty Period in a country and until the end of the Reduced Royalty Period, in lieu of the royalty rates set forth in TABLE 3 of Section 9.7.1, Roche will pay Ionis royalty rates (the "***Roche Reduced Royalty***") on Net Sales of Products in such country calculated on a Calendar Quarter-by-Calendar Quarter basis by *[***]*; *provided, however*, that the Roche Reduced Royalty rate in each country will in no event exceed the Reference Rate applicable under this Section 9.7. For example, if peak Calendar Year Net Sales of Products during the Full Royalty Period were US$[***] and royalties paid for that same Calendar Year were US$[***] resulting in a [***], and if [***] and the [***], the applicable [***] in such country would be [***]. Similarly, if the [***], then the applicable [***] in such country would be [***].

Notwithstanding anything to the contrary in this subsection (b), if, during the Reduced Royalty Period for a Product, Ionis (on its own or with a Third Party) following marketing approval sells an ASO designed to bind to the RNA that encodes Factor B in the Field, then such Reduced Royalty Period will end and Roche's worldwide license under Section 7.1.1 solely with respect to such Product will become fully paid-up and royalty-free.

(c) **Limitation on Aggregate Reduction for Roche Royalties**.

(i) In no event will the royalty reductions under Section 9.7.2(b) reduce the royalties payable to Ionis on Net Sales of the applicable Product in any given period to an amount that is less than the [***].

(ii) In no event will the aggregate royalty offsets under Section 9.10.3(b) reduce the royalties payable to Ionis on Net Sales of a Product in the applicable country in any given period to an amount that is less than the greater of (i) [***], and (ii) [***] for such Product in such country in such period.

(d) **End of Royalty Obligation**. On a country-by-country basis, other than [***], Roche's obligation to make royalty payments hereunder 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 [***] in such country and ending when the [***] is (i) with respect to Net Sales of Products in Major Markets, [***], and (ii) [***].

(e) **Royalty Examples**. Schedule 9.7.2(e) attached hereto contains examples of how royalties will be calculated under this Section 9.7.

(f) **Allocation of Net Sales**. If, by reason of one or more royalty rate adjustments under this Section 9.7.2, different royalty rates apply to Net Sales of Products from different countries, Roche will [***] such Net Sales [***]. SCHEDULE 9.7.2(f) attached hereto contains examples of how Net Sales of Products from different countries at different royalty rates will be [***].

9.8. **Apportionment of Compulsory Sublicensee Consideration**. At such time as Roche or any of its Affiliates or Sublicensees enters into a sublicense with a Compulsory Sublicensee, the Parties will discuss and mutually agree upon an adjustment of the royalty due to Ionis under Section 9.7 of this Agreement with respect to sales of Products by such Compulsory Sublicensee, with such adjustment calculated based on a [***].

9.9. **Reverse Royalty Payments to Roche for Discontinued Products**. If Ionis or any of its Affiliates or Sublicensees Commercializes a Discontinued Product for which Roche has paid Ionis the license fee under Section 9.3, then following the First Commercial Sale of such Discontinued Product by Ionis or its Affiliates or Sublicensees, Ionis will pay Roche a royalty of [***] of Annual worldwide net sales of such Discontinued Product ("***Ionis Product Reverse Royalties***"). Ionis will pay Roche such Ionis Product Reverse Royalties in accordance with the provisions governing payment of royalties from Roche to Ionis in Sections 9.7.2, 9.10, 9.11, 9.12, 9.13, and 9.14 (*mutatis mutandis*); *provided, however*, that Ionis' obligation to pay Roche Ionis Product Reverse Royalties will expire once Ionis has paid Roche an amount equal to [***] for such Discontinued Product under Section 9.4.

9.10. **Third Party Payment Obligations**.

9.10.1. **In-License Agreements**.

(a) ***Ionis' In-License Agreements between the Effective Date and the Time of Option Exercise***. Before Ionis enters into an in-license agreement with a Third Party that would impact the Developing, Manufacturing and/or Commercializing of a Product, Ionis will consult with Roche and discuss the terms and conditions of such license and seek Roche's permission to enter into such license, which will not be unreasonably denied, conditioned or delayed. Before Roche exercises the Option, Ionis will provide to Roche a final list of all agreements entered into after the Effective Date by Ionis with Third Party licensors or sellers under which Ionis licensed or acquired any Licensed Intellectual Property to be licensed to Roche under Section 7.1.1 ("***Additional Ionis In-License Agreements***"). Any payment obligations arising under any Additional Ionis In-License Agreements as they apply to Products that:

(i) accrue before Option exercise will be paid by [***] as [***]; and

(ii) accrue after Option exercise will be paid by [***] to [***] as [***], in which case Section 9.10.3 will apply.

(b) ***Roche's Existing In-License Agreements***. Roche will be solely responsible for any Third Party Obligations that become payable by Roche to Third Parties under any agreements or arrangements Roche has with such Third Parties as of the Effective Date, based on the Development or Commercialization of a Product by Roche, its Affiliate or Sublicensee under this Agreement. Any such payment obligations will be paid by [***] to such Third Parties pursuant to the applicable agreement.

9.10.2. New In-Licensed Product-Specific Patents.

(a) On a Product-by-Product basis, after Option exercise, Roche or Ionis, as the case may be, will provide the other Party written notice of any additional Third Party Patent Rights promptly after it has identified such Third Party Patent Rights as necessary to Develop or Commercialize a Product where such Third Party Patent Rights would be considered a Product-Specific Patent if either Party Controlled such Patent Rights ("***Additional Product-Specific Patents***"), and Roche will have the first right, but not the obligation, to negotiate with, and obtain a license from the Third Party Controlling such Additional Product-Specific Patents. If Roche obtains any such Additional Product-Specific Patents then any financial obligations under such Third Party agreement will be paid solely by [***] to the Third Party.

(b) If, however, Roche elects not to obtain such a license to such Additional Product-Specific Patents, Roche will so notify Ionis, and Ionis may obtain such a license to such Additional Product-Specific Patents and Ionis will include such Additional Product-Specific Patents in the license granted to Roche under Section 7.1.1 *provided that* Roche agrees in writing to [***].

9.10.3. Additional Core IP In-License Agreements.

(a) Roche will promptly provide Ionis written notice of any [***] ("***Additional Core IP***") that Roche 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. For clarity, Additional Core IP does not include any Patent Rights claiming (or intellectual property related to) [***]. If Ionis obtains such a Third Party license, Ionis will include such Additional Core IP in the license granted to Roche under Section 7.1.1, 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 Roche, and Roche may obtain such a Third Party license and, subject to Section 9.7.2(c)(ii), Roche may offset an amount equal to [***] of [***] paid by Roche under such Third Party license against any [***] of this Agreement in such country for [***].

(c) If Ionis does not agree with Roche that a license to such Third Party Patent Rights is necessary to [***], then Ionis will send written notice to such effect to Roche, and the Parties will engage a mutually agreed 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 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 Roche is permitted to [***]. The costs of any Third Party expert engaged under this Section 9.10.3(c) will be paid by the Party against whom the Third Party lawyer makes his or her determination.

9.11. Payments.

9.11.1. Commencement. Beginning with the Calendar Quarter in which the First Commercial Sale, named patient sale, compassionate use sale or other similar sales for a Product is made and for each Calendar Quarter thereafter, Roche will make royalty payments to Ionis under this Agreement within [***] following the end of each such Calendar Quarter.

9.11.2. Royalty Reporting. Each royalty payment will be accompanied by a report, summarizing in writing for the relevant Calendar Quarter on a Product-by-Product basis the following information:

(a) Sales in Swiss Francs on a country-by-country basis;

(b) Net Sales in Swiss Francs on a country-by-country basis;

(c) Total worldwide Net Sales in Swiss Francs;

(d) Exchange rate used for the conversion of Net Sales from Swiss Francs to U.S. Dollars pursuant to Section 9.11.4;

(e) Royalty rate pursuant to Section 9.7.1 and Section 9.7.2, as applicable; and

(f) Total royalty payable in U.S. Dollars.

In addition, Roche will include in each report under this Section 9.11.2 information regarding any Net Sales of Products sold for named patient, compassionate use or other similar sales and any consideration received from any Compulsory Sublicensees.

9.11.3. **No Payments and Estimates**. After first Approval, if no royalties or other payments from Product sales are payable in respect of a given Calendar Quarter, Roche 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 (or any named patient sale, compassionate use sale or other similar sales of a Product) is made and for each Calendar Quarter thereafter, within ten (10) Business Days following the end of each such Calendar Quarter, Roche will provide Ionis a [***] report estimating the total (A) Sales and Net Sales for Products projected for such Calendar Quarter, and (B) if available, the amount of any consideration payable to Roche under sublicenses with Compulsory Sublicensees.

9.11.4. **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) irrevocable and non-refundable. Any corrections to calculations of royalty payments previously paid will be adjusted to the next royalty payment due. When calculating the Sales of a Product that occur in currencies other than U.S. Dollars, Roche will convert the amount of such sales into Swiss Francs and then into U.S. Dollars using Roche's then current internal foreign currency translation actually used on a consistent basis in preparing its audited financial statements (currently YTD average rate as reported by Reuters).

9.11.5. **Records Retention**. Commencing with the First Commercial Sale or named patient sale of a Product, Roche 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 Roche hereunder.

9.12. **Audits**. After the first Approval of a Product, during the remaining Agreement Term and for a period of thirty-six (36) calendar months thereafter, at the request and expense of Ionis, Roche will permit an independent certified public accountant of internationally recognized standing appointed by Ionis, at reasonable times and upon at least sixty (60) Business Days written notice, but in no case more than once per Calendar Year, 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 thirty-six (36) calendar months for those countries specifically requested by Ionis. No Calendar Year can be audited more than once. Any and all records of Roche examined by such independent certified public accountant will be deemed Roche's Confidential Information. The independent certified public accountant will share all draft reports with Roche before sharing the draft audit report with Ionis and before issuing the final document. Upon completion of the audit, the accounting firm will provide both Roche and Ionis with a written report disclosing whether the calculation of Net Sales and royalty payments made by Roche are correct and the specific details concerning any discrepancies ("***Audit Report***"). If any Audit Report shows that Roche's payments under this Agreement were less than the royalty amount that should have been paid, then Roche will make all payments required to be made by paying Ionis the difference between such amounts to eliminate any discrepancy revealed by said inspection with the next royalty payment due, with interest calculated in accordance with Section 9.14. If any Audit Report shows that Roche's payments under this Agreement were greater than the royalty amount that should have been paid, then [***] or [***]. Ionis will pay all fees charged by such accountant pursuant to the audit, *except that*, if the audit determines that any additional amounts payable by Roche for an audited period exceed [***] of the amount actually paid for such audited period, then, in addition to paying Ionis any unpaid amounts discovered in such audit, Roche will pay the fees and expenses charged by such accountant.

9.13. **Taxes**.

9.13.1. **Taxes on Income**. Each Party will be solely responsible for the payment of all taxes imposed on its share of income arising directly or indirectly from the activities of the Parties under this Agreement.

9.13.2. **Withholding Tax**. To the extent the paying Party is required to deduct and withhold taxes 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 to secure an exemption from, or a reduction in, any withholding taxes, the Parties will provide such documentation to the extent they are able to do so. In accordance with the procedures set forth in Section 12.3, the receiving Party will also indemnify the paying Party for any tax, interest or penalties imposed on the paying Party if the paying Party improperly reduces or eliminates withholding tax based upon representations made by the receiving Party.

9.13.3. **Tax Cooperation**. At least fifteen (15) days prior to the date a given payment is due under this Agreement, the non-paying Party will provide the paying Party with any and all tax forms that may be reasonably necessary for the paying Party to lawfully not withhold tax or to withhold tax at a reduced rate with respect to such payment under an applicable bilateral income tax treaty. Following the paying Party's timely receipt of such tax forms from the non-paying Party, the paying Party 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. The non-paying Party will provide any such tax forms to the paying Party upon request and in advance of the due date. Each Party will provide the other with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding taxes resulting from payments made under this Agreement, such recovery to be for the benefit of the Party who would have been entitled to receive the money but for the application of withholding tax under this Section 9.13.

The provisions of this Section 9.13 are to be read in conjunction with the provisions of Section 15.4 below.

9.14. **Interest**. Any undisputed payments to be made hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest at a rate per annum equal to the lesser of (i) one month LIBOR rate in effect on the date that such payment would have been first due plus two percentage points (2%) or (ii) the maximum rate permissible under applicable law.

ARTICLE 10.
INTELLECTUAL PROPERTY

10.1. **Ownership**.

10.1.1. **Ionis Intellectual Property and Roche Intellectual Property**. 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 Roche will own and retain all of its rights, title and interest in and to the Roche Know-How and Roche Patents, subject to any assignments, rights or licenses expressly granted by one Party to the other Party under this Agreement.

10.1.2. **Agreement Intellectual Property**. Each Party will promptly disclose to the other Party in writing, and will cause its Affiliates to so disclose, the discovery, development, or creation of any invention made solely or jointly by the Parties in connection with the performance of obligations 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 Collaboration Intellectual Property 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.

10.1.3. **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 10. Ionis' obligation to participate in the JPC will terminate upon the date Ionis is no longer obligated to participate in the JSC. Thereafter, Ionis will have the right, but not the obligation, to participate in JPC meetings. If Ionis chooses not to participate, then Roche can dissolve the JPC. The JPC determines the invention classification for each invention arising under this Agreement. The classifications are (i) Ionis Product-Specific Patents, (ii) Ionis Collaboration Patents, (iii) Roche Collaboration Patents, (iv) Jointly-Owned Collaboration Patents, (v) Ionis Core Technology Patents, and (vi) Ionis Manufacturing and Analytical Patents. The JPC will endeavor to separate the claims within such Patent Rights into separate and distinct patent applications corresponding with the categories described in this Section 10.1.3(a) to the extent possible without diminishing the patentability of the inventions.

(b) A strategy will be discussed with regard to (x) prosecution and maintenance, defense and enforcement of (A) Ionis Product-Specific Patents, (B) Ionis Collaboration Patents, (C) Roche Collaboration Patents, and (D) Jointly-Owned Collaboration Patents licensed to Roche under Section 7.1.1 in connection with a Product, (y) defense against allegations of infringement of Third Party Patent Rights, and (z) licenses to Third Party Patent Rights or Know-How (including whether to obtain any licenses under any such Third-Party Patent Rights or Know-How, and whether there are any known Third Party Obligations applicable to a particular Product), in each case to the extent such matter would be reasonably likely to have a material impact on the Agreement or the licenses granted hereunder, which strategy will be considered in good faith by the Party entitled to prosecute, enforce and defend such Patent Rights hereunder, but will not be binding on such Party. Notwithstanding the above, subject to the provisions of Section 9.10, Roche will have final say as to whether to obtain any licenses under Third-Party Patent Rights or Know-How.

(c) In addition, the JPC will be responsible for the determination of inventorship. The determination of inventorship will be in accordance with United States patent laws and therefore will determine if the invention is solely or jointly owned by the relevant Party or Parties. In case of a dispute in the JPC (or otherwise between Ionis and Roche) over inventorship or classification, if the JPC cannot resolve such dispute, even after seeking the JSC'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 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 10. The JPC will determine by unanimous consent the JPC operating procedures at its first meeting. To the extent reasonably requested by either Party, the JPC will solicit the involvement of more senior members of their respective legal departments with respect to critical issues. 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.

10.2. Prosecution and Maintenance of Patents.

10.2.1. Patent Filings. The Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Section 10.2.2 and Section 10.2.3 will endeavor to obtain patent protection for a 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.

10.2.2. Licensed Patents and Roche Patents.

(a) Licensed Patents.

(i) Ionis Core and Manufacturing Patents. Ionis will at all times control and be responsible for all aspects of (i) the Ionis Core Technology Patents, and (ii) the Ionis Manufacturing and Analytical Patents.

(ii) Ionis Product-Specific Patents.

(1) ***Before Option Exercise***. Before Option exercise, subject to Section 10.2.3 and Section 10.2.4, at Ionis' expense, Ionis will control and be responsible for Prosecuting and Maintaining the Ionis Product-Specific Patents.

(2) ***After Option Exercise***. After Option exercise, subject to Section 10.2.3 and Section 10.2.4, at Roche's expense, so long as the applicable license to Roche under Section 7.1.1 is in effect, Roche will control and be responsible for all aspects of the Prosecution and Maintenance of all Ionis Product-Specific Patents (including any Jointly-Owned Collaboration Patents that are also Product-Specific Patents) Covering Products and will either (i) use commercially reasonably efforts to Prosecute and Maintain such Patent Rights or (ii) offer to assign Roche's entire right, title and interest in such Patent Rights to Ionis, in which case following any such assignment all licenses granted in this Agreement by Ionis to Roche under such Patent Rights will become non-exclusive and the exclusivity covenants under Section 5.1 will no longer apply to such Patent Rights.

(b) Roche Patents and Roche Collaboration Patents. Roche will control and be responsible for all aspects of the Prosecution and Maintenance of all Roche Patents and Roche Collaboration Patents, subject to Section 10.2.3 and Section 10.2.4.

10.2.3. **Jointly-Owned Collaboration Patents**. The Parties will decide through the JPC the appropriate Party to control and be responsible for Prosecuting and Maintaining all Jointly-Owned Collaboration Patents not provided for above.

10.2.4. **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 Product-Specific Patents or Jointly-Owned Collaboration Patents for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 10.2.2 or this Section 10.2.4, 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 Roche elects (i) not to file and prosecute patent applications for the Jointly-Owned Collaboration Patents or Ionis Product-Specific Patents that have been licensed to Roche under this Agreement for which Roche has responsibility for Prosecution and Maintenance pursuant to Section 10.2.2 or Section 10.2.3 ("***Roche-Prosecuted Patents***") in a particular country, (ii) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) or maintenance of any Roche-Prosecuted Patent in a particular country, or (iii) not to file and prosecute patent applications for the Roche-Prosecuted Patent in a particular country following a written request from Ionis to file and prosecute in such country, then Roche will so notify Ionis promptly in writing of its intention 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 Ionis will have the right, but not the obligation, to file, prosecute, maintain, enforce, or otherwise pursue such Roche-Prosecuted Patent in the applicable country at its own expense with counsel of its own choice. In such case, Roche will cooperate with Ionis to file for, or continue to Prosecute and Maintain or enforce, or otherwise pursue such Roche-Prosecuted Patent in such country. Notwithstanding anything to the contrary in this Agreement, if Ionis assumes responsibility for the Prosecution and Maintenance of any such Roche-Prosecuted Patent under this Section 10.2.4(b), Ionis will have no obligation to notify Roche if Ionis intends to abandon such Roche-Prosecuted Patent. The analogous situation will apply *mutatis mutandis* with regard to Patent Rights (excluding Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents) for which Ionis has responsibility for Prosecution and Maintenance pursuant to Section 10.2.2 or Section 10.2.3.

(c) 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 Jointly-Owned Collaboration 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.

(d) If the Party responsible for Prosecution and Maintenance pursuant to Section 10.2.3 intends to abandon such Jointly-Owned Collaboration Patent without first filing a continuation or substitution, then such Party will notify the other Party of such intention at least sixty (60) days before such Jointly-Owned Collaboration 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 10.3.1) 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 Collaboration Patents. If a Party assumes responsibility for the Prosecution and Maintenance of any such Jointly-Owned Collaboration Patents under this Section 10.2.4(d), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Collaboration Patents.

(e) 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.

10.3. Patent Costs.

10.3.1. Jointly-Owned Collaboration Patents. Unless the Parties agree otherwise, Ionis and Roche will share equally the Patent Costs associated with the Prosecution and Maintenance of Jointly-Owned Collaboration Patents; *provided that*, either Party may decline to pay its share of costs for filing, prosecuting and maintaining any Jointly-Owned Collaboration 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, title and interest in and to such Jointly-Owned Collaboration Patents.

10.3.2. **Licensed Patents and Roche Patents**. Except as set forth in Section 10.2.4 and Section 10.3.1, 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 10.2; *provided, however*, that after Option exercise, Roche will be solely responsible for Patent Costs arising from the Prosecution and Maintenance of the Ionis Product-Specific Patents; *provided that*, Roche may decline to pay for filing, prosecuting and maintaining any such Ionis Product-Specific Patents in a particular country or particular countries, in which case all licenses granted in this Agreement by Ionis to Roche under such Patent Rights will become non-exclusive and the exclusivity covenants under Section 5.1 will no longer apply to such Patent Rights.

10.4. **Defense of Claims Brought by Third Parties**.

10.4.1. 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 Option exercise at its sole cost and expense and (b) Roche will have the first right, but not the obligation, to defend against any such Proceeding initiated after Option exercise at its sole cost and expense. If the Party having the first right to defend against such Proceeding (the "***Lead Party***") elects to defend against such Proceeding, then the Lead Party will have the sole right to direct the defense and to elect whether to settle such claim (but only with the prior written consent of the other Party, not to be unreasonably withheld, conditioned or delayed). The other Party will reasonably assist the Lead Party in defending such Proceeding and cooperate in any such litigation at the request and expense of the Lead Party. The Lead Party will provide the other Party with prompt written notice of the commencement of any such Proceeding that is of the type described in this Section 10.4, 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 sixty (60) days after the Lead Party first receives written notice of the initiation of such Proceeding, and the other Party (the "***Step-In Party***") will have the right, but not the obligation, to defend against such Proceeding at its sole cost and expense and thereafter the Step-In Party will have the sole right to direct the defense thereof, including the right to settle such claim. In any event, the Party not defending such Proceeding will reasonably assist the other Party and cooperate in any such litigation at the request and expense of the Party defending such Proceeding. Each Party may at its own expense and with its own counsel join any defense initiated or directed by the other Party under this Section 10.4. Each Party will provide the other Party with prompt written notice of the commencement of any such Proceeding under this Section 10.4, 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.

10.4.2. **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. Roche 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 Roche 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 10.4.2, and Ionis will promptly furnish Roche with a copy of each communication relating to the alleged infringement received by Ionis.

10.4.3. **Interplay Between Enforcement of IP and Defense of Third Party Claims**. Notwithstanding the provisions of Section 10.4.1 and Section 10.4.2, to the extent that a Party's defense against a Third Party claim of infringement under this Section 10.4 involves (i) the enforcement of the other Party's Know-How or Patent Rights, or (ii) the defense of an invalidity claim with respect to such other Party's Know-How or Patent Rights, then, in each case, the general concepts of Section 10.5 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 10.5, 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 10.5, to enforce such Know-How or Patent Rights or defend such invalidity claim).

10.5. **Enforcement of Patents Against Competitive Infringement**.

10.5.1. **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 Factor B 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 10.5.7 below, such written notice will be given within ten (10) Business Days.

10.5.2. **Before Option Exercise**. For any Competitive Infringement occurring after the Effective Date but before Option exercise, 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 Roche 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 Roche with prompt written notice of the commencement of any such Proceeding, and Ionis will keep Roche apprised of the progress of such Proceeding. If Ionis fails to initiate a Proceeding within a period of ninety (90) days after receipt of written notice of such Competitive Infringement (subject to a ninety (90)-day extension to conclude negotiations, which extension will apply only if Ionis has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such ninety (90)-day period), Roche 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 10.5.2 to the extent involving any Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents.

10.5.3. **After Option Exercise**. For any Competitive Infringement with respect to a Product (except for a Discontinued Product) occurring after Option exercise, so long as part of such Proceeding Roche also enforces any Patent Rights Controlled by Roche being infringed that Cover a Product, then Roche 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*, Roche will have the right to control such litigation. If Roche fails to initiate a Proceeding within a period of ninety (90) days after receipt of written notice of such Competitive Infringement (subject to a 90-day extension to conclude negotiations, if Roche has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such ninety (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 Roche 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 10.5.3 to the extent involving any Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents.

10.5.4. **Joinder**.

(a) If a Party initiates a Proceeding in accordance with this Section 10.5, 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 10.5.5, the costs and expenses of each Party incurred pursuant to this Section 10.5.4(a) will be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 10.5, 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.

10.5.5. **Share of Recoveries**. Any damages or other monetary awards recovered with respect to a Proceeding brought pursuant to this Section 10.5 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 before Roche's exercise of the Option will be (i) [***]; or (ii) [***]; then

(c) any remaining proceeds constituting direct or actual damages for acts of infringement occurring after Roche's exercise of the Option will be treated [***], and [***]; 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.

10.5.6. **Settlement**. Notwithstanding anything to the contrary under this ARTICLE 10, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this ARTICLE 10 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.

10.5.7. **35 U.S.C. § 271(e)(2) Infringement**. Notwithstanding anything to the contrary in this Section 10.5, solely with respect to Licensed Patents, for a Competitive Infringement under 35 U.S.C. § 271(e)(2), the time period set forth in Section 10.5.2 during which a Party will have the initial right to bring a Proceeding will be shortened to a total of twenty-five (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 twenty-five (25) days after such first Party's receipt of written notice of such Competitive Infringement.

10.6. **Other Infringement**.

10.6.1. **Jointly-Owned Collaboration Patents**. With respect to the infringement of a Jointly-Owned Collaboration 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 10.6.1 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 will retain the remainder of such proceeds, 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 10.6.1, [***] of such proceeds; and (B) if only one Party initiates the Proceeding pursuant to this Section 10.6.1, such Party will receive [***] of such proceeds and the other Party will receive [***] of such proceeds.

10.6.2. **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.

10.6.3. **Patents Solely Owned by Roche**. Roche will retain all rights to pursue an infringement of any Patent Right solely owned by Roche which is other than a Competitive Infringement and Roche will retain all recoveries with respect thereto.

10.7. **Patent Listing**.

10.7.1. **Roche's Obligations**. Roche 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 JPC, to evaluate and identify all applicable Patent Rights, and Roche 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, Roche will retain final decision-making authority as to the listing of all applicable Patent Rights for a Product that are not Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents, regardless of which Party owns such Patent Rights.

10.7.2. **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.

10.8. **Joint Research Agreement under the Leahy-Smith America Invents Act**. If a Party intends to invoke its rights under 35 U.S.C. § 102(c) of the Leahy-Smith America Invents Act, it will notify the other Party and neither Party will make an election under such provision when exercising its rights under this ARTICLE 10 without the prior written consent of the other Party (such consent not to be unreasonably withheld, conditioned or delayed), and the Parties will use reasonable efforts to cooperate and coordinate their activities with such Party with respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "*joint research agreement*" as defined in 35 U.S.C. § 100(h).

10.9. **Obligations to Third Parties**. Notwithstanding any of the foregoing, each Party's rights and obligations with respect to Licensed Intellectual Property under this ARTICLE 10 will be subject to the Third Party rights and obligations under any (i) Third Party agreements for Additional Product-Specific Patents, the restrictions and obligations of which Roche has agreed to under Section 9.10.2(b), (ii) the Prior Agreement, and (iii) Additional 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 Roche hereunder and this Agreement purports to grant any such rights to Roche, Ionis will act in such regard with respect to such Patent Rights at Roche's direction.

10.10. **Additional Right and Exceptions**. Notwithstanding any provision of this ARTICLE 10, but subject to Section 10.4.3, 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. If Ionis determines, in Ionis' sole discretion, not to enforce any Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents and does not permit Roche to so enforce such Patent Rights, then the Parties will mutually agree on an appropriate adjustment (if any) of the future consideration payable by Roche under this Agreement to reflect any adverse impact Ionis' failure to enforce such Patent Rights has on Products.

10.11. **Patent Term Extension**. The Parties will cooperate with each other in gaining patent term extension wherever applicable to a Product, including European supplementary protection certificates and pediatric exclusivity. After exercising the Option, Roche will determine which Ionis Product-Specific Patents and Jointly Owned Collaboration Patents that are also Product-Specific Patents will be extended and what extensions will be sought.

10.12. **No Challenge**. If, during the Agreement Term, solely with respect to rights to the Ionis Product-Specific Patents that are included (or, prior to Option exercise, are eligible to be included) in a license granted to Roche under Section 7.1.1, Roche, its Affiliates or Sublicensees, in any country, (a) commence or otherwise voluntarily determine to participate in (other than 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) any action or proceeding, challenging or denying the enforceability or validity of any claim within an issued patent or patent application within such Ionis Product-Specific Patents, or (b) direct, support or actively assist any other Person (other than 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) 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 Ionis Product-Specific Patents, then unless, within thirty (30) days after written notice from Ionis, Roche rescinds any actions brought by Roche, its Affiliates, or Sublicensees, Ionis may, to the extent permitted under Applicable Law, terminate this Agreement and the provisions of Section 13.4.1 and Section 13.4.2 will apply; *[***]*.

ARTICLE 11.
REPRESENTATIONS AND WARRANTIES

11.1. **Representations and Warranties of Both Parties**. Each Party hereby represents and warrants to the other Party, as of the Effective Date, that:

11.1.1. 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;

11.1.2. 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;

11.1.3. 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;

11.1.4. 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 to the best of its knowledge and belief violate any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over such Party;

11.1.5. to the best of its knowledge and belief, other than with respect to the HSR Act, 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

11.1.6. it has not employed (and, to the best of its knowledge and belief, 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 Non-Clinical Studies or Clinical Studies of a Product and its activities under the Development Plan.

11.2. **Representations and Warranties of Ionis**. Ionis hereby represents and warrants to Roche, as of the Effective Date, that:

11.2.1. To the best of its knowledge and belief, there are no additional licenses under any intellectual property owned or Controlled by Ionis or its Affiliates as of the Effective Date that would be required in order for Roche to further Develop and Commercialize a Product existing on the Effective Date.

11.2.2. The Licensed Intellectual Property 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 Products existing on the Effective Date in the Field. Ionis has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in the Licensed Intellectual Property in a manner that conflicts with any rights granted to Roche hereunder.

11.2.3. 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 Licensed Intellectual Property 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 Licensed Intellectual Property that would impact activities under this Agreement.

11.2.4. SCHEDULE 11.2.4(a), SCHEDULE 11.2.4(b) and SCHEDULE 11.2.4(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 Products as of the Effective Date, 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 Roche under this Agreement.

11.2.5. (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, (d) none of the Ionis Product-Specific Patents that would be licensed by Ionis to Roche upon Option exercise under this Agreement 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, and (e) to the best of Ionis' knowledge and belief, Roche's practice of the inventions claimed in the Ionis Product-Specific Patents in the performance of the Development Plan contemplated as of the Effective Date will not [***].

11.2.6. SCHEDULE 11.2.6 is a complete and accurate list of the one Prior Agreement, which is the only agreement that creates Third Party Obligations that affect the rights granted by Ionis to Roche under this Agreement. Ionis is not in default of such Prior Agreement, and the applicable Third Party, to the best knowledge of Ionis, has no grounds upon which to claim that Ionis is in default that would affect the rights granted by Ionis to Roche under this Agreement. To the best knowledge of Ionis, the applicable Third Party is not in default with respect to a material obligation under such Prior Agreement that would adversely impact activities under this Agreement.

11.2.7. Ionis has all rights necessary to grant the option and licenses contained in this Agreement, and has the ability to work exclusively with Roche as set forth in this Agreement, including the covenants granted in Section 5.1.

11.3. **Ionis Covenants**. Ionis hereby covenants to Roche that, except as expressly permitted under this Agreement:

11.3.1. Ionis will promptly amend SCHEDULE 11.2.4(a), SCHEDULE 11.2.4(b) and SCHEDULE 11.2.4(c) and submit such amended Schedules to Roche 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.

11.3.2. during the Agreement Term, Ionis will maintain and not breach (i) the Prior Agreement, (ii) any Additional Ionis In-License Agreements (if any), and (iii) any agreements with Third Parties entered into after the Option exercise (including Third Party agreements for Additional Product-Specific Patents described in Section 9.10.2(b) 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 Roche for a Product under this Agreement (collectively (i), (ii), and (iii), "***New Third Party Licenses***");

11.3.3. Ionis will promptly notify Roche 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 Roche to cure such breach on Ionis' behalf upon Roche's request;

11.3.4. Ionis will not amend, modify or terminate any New Third Party License in a manner that would adversely affect Roche's rights hereunder without first obtaining Roche's written consent, which consent may be withheld in Roche's sole discretion;

11.3.5. 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 Roche under this Agreement;

11.3.6. Ionis will cause its Affiliates, licensees and sublicensees to comply with the terms of Section 5.1;

11.3.7. 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 (or grant a license to Ionis or an option to obtain such a license) developed by them, whether or not patentable, to Ionis or such Affiliate, respectively, as the sole owner thereof; and

11.3.8. 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 Roche to further Develop, Manufacture or Commercialize a Product, and Roche has exercised its Option and the license granted to Roche under this Agreement is in effect, Ionis will make such technology available to Roche on commercially reasonable terms.

11.4. **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. ROCHE AND IONIS UNDERSTAND THAT PRODUCTS ARE THE SUBJECT OF ONGOING RESEARCH AND DEVELOPMENT AND THAT NEITHER PARTY CAN ASSURE THE SAFETY, USEFULNESS OR COMMERCIAL OR TECHNICAL VIABILITY OF THE PRODUCTS.**

ARTICLE 12.
INDEMNIFICATION; INSURANCE

12.1. **Indemnification by Roche**. Roche 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:

12.1.1. the gross negligence or willful misconduct of Roche, its Affiliates or Sublicensees and its or their respective directors, officers, employees and agents, in connection with Roche's performance of its obligations or exercise of its rights under this Agreement;

12.1.2. any breach of any representation or warranty or express covenant made by Roche under ARTICLE 11 or any other provision under this Agreement;

12.1.3. the Development or Manufacturing activities that are conducted by or on behalf of Roche 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

12.1.4. the Commercialization of a Product by or on behalf of Roche 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 12.2.

12.2. **Indemnification by Ionis**. Ionis will indemnify, defend and hold harmless Roche 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:

12.2.1. 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;

12.2.2. any breach of any representation or warranty or express covenant made by Ionis under ARTICLE 11 or any other provision under this Agreement;

12.2.3. 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 Roche pursuant to this Agreement); or

12.2.4. any development, manufacturing or commercialization activities that are conducted by or on behalf of Ionis or its Affiliates or Sublicensees with respect to a Product or 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 Roche or its Affiliates, licensees, Sublicensees or contractors and its or their respective directors, officers, employees and agents or other circumstance for which Roche has an indemnity obligation pursuant to Section 12.1.

12.3. **Procedure**. If a Person entitled to indemnification under Section 12.1 or Section 12.2 (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* 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), (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 10.4 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 12.1 or Section 12.2, as the case may be, for Claims settled or compromised by the Indemnitee without the indemnifying Party's prior written consent.

12.4. Insurance.

12.4.1. Ionis' Insurance Obligations. Ionis will maintain, at its cost, reasonable insurance against liability and other risks associated with its activities contemplated by this Agreement (including product liability for a Discontinued Product), including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for biotech companies of similar size and with similar resources in the pharmaceutical industry for the activities to be conducted by it under this Agreement taking into account the scope of development of products. Ionis will maintain such insurance throughout the Agreement Term and for five (5) years thereafter, and Ionis will furnish to Roche evidence of any insurance required under this Section 12.4.1, upon request.

12.4.2. Roche's Insurance Obligations. Roche hereby represents and warrants to Ionis that it will maintain, at its cost, reasonable insurance or self-insure against liability and other risks associated with its activities contemplated by this Agreement (including product liability), including but not limited to its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices for large companies in the pharmaceutical industry for the activities to be conducted by Roche under this Agreement. Roche will maintain such self-insurance throughout the Agreement Term and for five years thereafter, and will furnish to Ionis evidence of such insurance, upon request.

12.5. LIMITATION OF CONSEQUENTIAL DAMAGES. EXCEPT FOR (a) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 12, (b) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT OF THIS AGREEMENT, (c) A PARTY'S BREACH OF ARTICLE 5, (d) A BREACH OF SECTION 13.4.1(b) BY ROCHE OR ITS AFFILIATES OR (e) 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, 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 13.
TERM; TERMINATION

13.1. **Agreement Term; Expiration**. This Agreement is effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this ARTICLE 13, will continue in full force and effect until this Agreement expires as follows:

13.1.1. on a country-by-country and Product-by-Product basis, on the date of expiration of all payment obligations by the Commercializing Party under this Agreement with respect to such Product (or such Discontinued Product) in such country; and

13.1.2. in its entirety upon the expiration of all payment obligations under this Agreement with respect to the last Product (or last Discontinued Product) in all countries pursuant to Section 13.1.1; and

13.1.3. where Roche has not provided Ionis a written notice stating Roche is exercising its Option under Section 6.1 by the Option Deadline.

The period from the Effective Date until the date of expiration of this Agreement pursuant to this Section 13.1 is the "***Agreement Term***". On a Product-by-Product basis, if with respect to a particular Product this Agreement expires (i.e., is not terminated early) under Section 13.1.1 or Section 13.1.2 in a particular country, then, effective upon such expiration, Ionis will and hereby does grant to Roche a fully paid-up and irrevocable non-exclusive, sublicensable license under the Licensed Intellectual Property to Manufacture, Develop and Commercialize the Product that is the subject of such expiration in such country.

13.2. **Termination of the Agreement**.

13.2.1. **Roche's Termination for Convenience**. After payment by Roche of the option fee under Section 9.1, subject to Section 13.4.1 below, Roche may terminate this Agreement in its entirety or in part on a country-by-country or Product-by-Product basis for convenience by providing (i) ninety (90) days' written notice to Ionis of such termination if the Product has not been sold commercially, or (ii) one hundred eighty (180) days' written notice to Ionis of such termination if the Product has been sold commercially.

13.2.2. **Termination for Material Breach**.

(a) **Roche's Right to Terminate**. If Roche believes that Ionis is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 3.1, which is governed by Section 13.2.3 below), then Roche may deliver notice of such material breach to Ionis. If the breach is curable, Ionis will have sixty (60) days to cure such breach. If Ionis fails to cure such breach within the sixty (60)-day period, or if the breach is not subject to cure, Roche may terminate this Agreement by providing written notice to Ionis.

(b) **Ionis' Right to Terminate**. If Ionis believes that Roche is in material breach of this Agreement (other than with respect to a failure to use Commercially Reasonable Efforts under Section 3.1 or Section 8.1, which is governed by Section 13.2.3 below), then Ionis may deliver notice of such material breach to Roche. If the breach is curable, Roche will have sixty (60) days to cure such breach (except to the extent such breach involves the failure to make a payment when due, which breach must be cured within thirty (30) days following such notice). If Roche fails to cure such breach within the sixty (60)-day or thirty (30)-day period, as applicable, or if the breach is not subject to cure, Ionis may terminate this Agreement by providing written notice to Roche.

13.2.3. Remedies for Failure to Use Commercially Reasonable Efforts.

(a) If Ionis, in Roche's reasonable determination, fails to use Commercially Reasonable Efforts to conduct the activities Ionis agreed to perform under Section 3.1 prior to Option exercise, Roche will notify Ionis and, within thirty (30) days thereafter, Ionis and Roche 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 for such activities in Section 3.1. Following such a meeting, if Ionis fails to use Commercially Reasonable Efforts as contemplated by Section 3.1, then subject to Section 13.2.4 below, Roche will have the right, at its sole discretion, to (i) terminate this Agreement, or (ii) prior to Option exercise, Roche may elect to trigger the alternative remedy provisions of Section 13.3 below, which such election is Roche's sole and exclusive remedy if Ionis fails to use Commercially Reasonable Efforts in the activities contemplated in Section 3.1 prior to Option exercise.

(b) If Roche, in Ionis' reasonable determination, fails to use Commercially Reasonable Efforts under Section 3.1 or Section 8.1 above, Ionis will notify Roche and, within thirty (30) days thereafter, Ionis and Roche 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 Roche's use of Commercially Reasonable Efforts under Section 3.1 or Section 8.1. Following such a meeting, if Roche fails to use Commercially Reasonable Efforts as contemplated by Section 3.1 or Section 8.1, then subject to Section 13.2.4 below, Ionis will have the right, at its sole discretion, to terminate this Agreement.

13.2.4. Disputes Regarding Material Breach. Notwithstanding the foregoing, if the Breaching Party in Section 13.2.2 or Section 13.2.3 disputes in good faith the existence, materiality, or failure to cure of any such breach which is not a payment breach, and provides notice to the Non-Breaching Party of such dispute within such sixty (60)-day period, the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 13.2.2 or Section 13.2.3, or trigger the alternative remedy provisions of Section 13.3, as applicable, unless and until it has been determined in accordance with Section 15.1 that this Agreement was materially breached by the Breaching Party and the Breaching Party fails to cure such breach within thirty (30) days following such determination. During the pendency of such dispute, all the terms 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.

13.2.5. 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 is served with an involuntary petition against it, filed in any insolvency proceeding, and such petition is not dismissed within ninety (90) days after the filing thereof; or if the other Party is a party to any dissolution or liquidation; or if the other Party makes 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.

13.3. Alternative Remedy to Termination Available to Roche Prior to Option Exercise. If Roche elects, pursuant to Section 13.2.3(a)(ii), to exercise the alternative remedy provisions of this Section 13.3 in lieu of terminating this Agreement by providing written notice of such election to Ionis in accordance with Section 13.2.3(a), then this Agreement will continue in full force and effect with the following modifications:

(a) Ionis will have no further obligations under the Development Plan, and Roche is responsible for the continued Development and Commercialization of IONIS-FB-L_{Rx} (including meeting all remaining performance obligations under Section 8.1);

(b) effective as of the date of Roche's notice to Ionis electing the alternative remedy provisions of this Section 13.3, Roche will be deemed for all purposes of this Agreement to have exercised the Option;

(c) Roche will have and Ionis grants, the exclusive license under Section 7.1.1;

(d) Ionis will perform its obligations under Section 7.2, assign and transfer the IND for IONIS-FB-L_{Rx} to Roche, and transfer, at Roche's request, any Phase 2 Trials then-being administered by Ionis, all within ninety (90) days after Roche electing to exercise its alternative remedies under this Section 13.3; and

(e) the financial provisions of ARTICLE 9 will be modified as follows:

(i) Roche will [***]; and

(ii) [***], Roche will [***], and the license fee set forth in Section 9.3 will be [***].

The milestone provisions of Section 9.4 and Section 9.5 and the royalty provisions of Section 9.7 will [***].

13.4. Consequences of Termination or Expiration of the Agreement.

13.4.1. In General. If this Agreement is terminated by a Party in accordance with Section 10.12 or this ARTICLE 13 in its entirety or on a country-by-country or Product-by-Product basis at any time and for any reason, the following terms will apply to any such termination:

(a) **Return of Information and Materials**. After termination of the Agreement, 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 that are the subject of such termination. 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) **License Termination**. Upon termination but not expiration of the Agreement, except for the licenses granted under Section 7.1.2 or, if applicable, Section 13.1, any licenses granted by Ionis to Roche under this Agreement will terminate and Roche, its Affiliates and Sublicensees will cease selling all Products that are the subject of such termination, unless Ionis elects to have Roche continue to sell the applicable Product(s) as part of the Transition Activities under Section 13.4.2(i).

(c) **Exclusivity Covenants**. Upon termination of this Agreement for any reason or expiration of this Agreement, neither Party will have any further obligations under Section 5.1 of this Agreement.

(d) **Development Plan**. Upon termination of this Agreement for any reason or expiration of this Agreement, neither Party will have any further obligations under the Development Plan or IDCP.

(e) **Accrued Rights**. Termination of this Agreement for any reason or expiration of this Agreement will be without prejudice to any rights or financial compensation that will have accrued to the benefit of a Party prior to such termination. Such termination will not relieve a Party from obligations that are expressly indicated to survive the termination of this Agreement. For purposes of clarification, milestone payments under ARTICLE 9 accrue as of the date the applicable Milestone Event is achieved even if the payment is not due at that time.

(f) **Survival**. The following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 7.1.2 (Cross Licenses under Collaboration Intellectual Property); Section 7.1.4(d) (Effect of Termination on Sublicenses), Section 7.2 (Technology Transfer) (but only to the extent necessary to satisfy the requirements of Section 13.4.2), Section 9.9 (Reverse Royalty Payments to Roche for a Discontinued Product), Section 9.11.5 (Records Retention), Section 9.12 (Audits), Section 10.1.1 (Ionis Intellectual Property and Roche Intellectual Property), Section 10.1.2 (Agreement Intellectual Property), Section 10.4.2 (Discontinued Product), Section 11.4 (Disclaimer), ARTICLE 12 (Indemnification; Insurance), Section 13.1 (Agreement Term; Expiration), Section 13.4 (Consequences of Expiration or Termination of the Agreement), ARTICLE 14 (Confidentiality), ARTICLE 15 (Miscellaneous) and APPENDIX 1 (Definitions) (to the extent definitions are embodied in the foregoing listed Articles and Sections).

13.4.2. **Special Consequences of Expiration or Termination of the Agreement**. If (A) this Agreement expires due to the expiration of Roche's Option under Section 6.2, (B) Roche terminates the Agreement under Section 13.2.1 (Roche's Termination for Convenience), or (C) Ionis terminates this Agreement under Section 10.12 (No Challenge), Section 13.2.2(b) (Ionis' Right to Terminate) or Section 13.2.3(b) (Remedies for Failure to Use Commercially Reasonable Efforts), then, *[***]* the following additional terms will also apply:

(a) ***License to Ionis for Discontinued Products***. Roche will and hereby does grant to Ionis a sublicensable, worldwide, exclusive license or sublicense, as the case may be, under all Roche Collaboration Intellectual Property created pursuant to activities under this Agreement (excluding Companion Diagnostic IP) as of the date of such reversion that Covers Discontinued Products solely as necessary to Develop, make, have made, use, sell, offer for sale, have sold, import and otherwise Commercialize such Discontinued Products in the Field;

(b) ***License to Ionis for Companion Diagnostic Products***. Roche will make available to Ionis, on commercially reasonable terms, (i) any Discontinued Product-specific diagnostic products and/or services offered by Roche as of the date of such reversion to patients who use the Discontinued Product (each, a "***Companion Diagnostic Product***") and (ii) any Patent Rights and Know-How Covering such Companion Diagnostic Products (such intellectual property, "***Companion Diagnostic IP***") Controlled by Roche as of the date of such reversion that is necessary to Develop or continue to Commercialize such Companion Diagnostic Products;

(c) ***Know-How Transfer***. Within ninety (90) days following the date of termination, Roche will transfer to Ionis for use with respect to the Development and Commercialization of Discontinued Products, copies of any Collaboration Know-How data, results, and regulatory information, and to the extent solely related to the Discontinued Products, pricing and market access strategy information, health economic study information, material communications with payors, filings, and files in the possession of Roche as of the date of such reversion that relate to such Discontinued Products and are necessary for the Development of such Discontinued Products, and any other information or material specified in Section 7.2;

(d) ***Regulatory Materials***. Within ninety (90) days following the date of the termination, Roche will assign, and hereby does assign, to Ionis all of Roche's right, title and interest in and to all Regulatory Materials for the Discontinued Product, including any IND, orphan drug designation and marketing authorizations that relate to the applicable Discontinued Product;

(e) ***Trademarks***. Roche will license to Ionis any trademarks that are specific to Discontinued Products solely for use with such Discontinued Products; *provided, however*, that in no event will Roche have any obligation to license to Ionis any trademarks used by Roche both in connection with a Product and in connection with the sale of any other product or service, including any Roche- or Roche-formative marks, company logos, or trademarks of its Affiliates or Sublicensees;

(f) ***Prosecution and Maintenance***. Ionis will control and be responsible at its sole cost for all aspects of the Prosecution and Maintenance of all Jointly-Owned Collaboration Patents, and Roche will provide Ionis with (and will instruct its counsel to provide Ionis with) all of the information and records in Roche's and its counsel's possession related to the Prosecution and Maintenance of such Jointly-Owned Collaboration Patents;

(g) ***Stocks of API and Finished Drug Product***. Ionis will have the right to purchase from Roche any or all of the inventory of API and/or Finished Drug Product for such Discontinued Product held by Roche as of the effective date of termination (that are not committed to be supplied to any Third Party or Sublicensee, in the ordinary course of business, as of the effective date of termination), if any, at a price equal to [***] to acquire or manufacture such inventory. Ionis will notify Roche within forty-five (45) days after the effective date of termination whether Ionis elects to exercise such right;

(h) ***Manufacturing Technology Transfer***. If Roche or Roche's CMO is manufacturing API and/or Finished Drug Product as of the termination triggering this provision, Ionis may request Roche to conduct (or cause to be conducted by Roche's CMO) a technology transfer to Ionis (or Ionis' designated Third Party supplier) of any technology, information and data reasonably related to Roche's or such CMO's manufacturing and supply of API and/or Finished Drug Product for such Discontinued Product, and if so requested, Roche will conduct (or cause to be conducted by Roche's CMO) such a technology transfer, and Ionis will [***], and Roche will (or will cause Roche's CMO to) continue to (i) provide reasonable support and cooperation with Ionis' regulatory filings and interactions with Regulatory Authorities related to Roche's or such CMO's API and/or Finished Drug Product manufacturing (including any required inspections), and (ii) supply (or cause to be supplied by Roche's CMO) API and/or Finished Drug Product to Ionis, at a price equal to [***] to enable Ionis to identify and contract with a suitable Third Party API and/or Finished Drug Product manufacturer; and

(i) ***Transition Activities***.

For a period of up to [***] following the effective date of termination:

(i) The Parties wish to provide a mechanism to ensure that, assuming the Discontinued Product is available to patients as of the reversion date, patients who were being treated with the Discontinued Product prior to such termination or who desire access to the Discontinued Product can continue to have access to such Discontinued Product while the regulatory and commercial responsibilities for the Discontinued Product are transitioned from Roche to Ionis. As such, Ionis may request Roche to perform transition activities that are necessary or useful to (1) transition Roche's Commercialization activities (if any) to Ionis to minimize disruption to sales, (2) provide patients with continued access to the applicable Discontinued Products (if applicable), (3) enable Ionis (or Ionis' designee) to assume and execute the responsibilities under all Approvals and ongoing Clinical Studies for the applicable Discontinued Product, and (4) ensure long-term continuity of supply for the Discontinued Product (collectively, the "***Transition Activities***"), including, if applicable, the categories of services and deliverables listed on SCHEDULE 13.4.2(i), but no longer than [***] following the effective date of termination. If applicable, Roche will perform such Transition Activities using commercially reasonable efforts for the periods set forth in SCHEDULE 13.4.2(i); provided Roche and Ionis may mutually agree in writing to conduct the Transition Activities for a longer period of time.

(ii) Ionis may elect to have Roche perform the applicable Transition Activities by providing written notice to Roche no later than forty-five (45) days following the effective date of the termination. If Ionis requests Transition Activities, without limiting the provisions of Section 13.4.2, the Parties will mutually agree upon a transition plan for Roche to perform the applicable Transition Activities including delivery and transition dates. In addition, the Parties will 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 Discontinued Product prior to the termination, and up to two (2) additional representatives from each Party who are from other relevant functional groups to facilitate a smooth transition. While Roche is providing applicable Transition Activities, Roche and Ionis will agree on talking points and a communication plan to customers, specialty pharmacies, physicians, regulatory authorities, patient advocacy groups, and clinical study investigators, in each case only if applicable at the time of reversion, and Roche will make all such communications to such applicable entities in accordance with the mutually agreed talking points.

(iii) Ionis will [***] to perform the Transition Activities. In addition, Ionis will [***] to perform the Transition Activities. Ionis will own [***].

ARTICLE 14.
CONFIDENTIALITY

14.1. **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***").

14.2. **Prior Confidentiality Agreement**. The Non-Disclosure Agreement executed by Ionis and Roche on February 7, 2018 (including any and all amendments thereto) (the "***CDA***") will terminate as of the Effective Date. All Confidential Information exchanged between the Parties under the CDA and on or after the Effective Date under this Agreement will be subject to the terms of this ARTICLE 14.

14.3. **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,* a Receiving Party may disclose Confidential Information 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 14.4 below), complying with applicable governmental regulations, obtaining Approvals, conducting Non-Clinical Studies or Clinical Studies, marketing a 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.

14.4. **Press Release; Publications; Disclosure of Agreement**.

14.4.1. **Public Announcements – Generally**. Upon execution of this Agreement, Ionis may issue a press release announcing the existence of this Agreement in a form and substance agreed to in writing 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 14.4, each Party agrees not to issue any other press release or other public statement disclosing other information relating to this Agreement or the terms of this Agreement or the transactions contemplated hereby without the prior written consent of the other Party, which consent will not be unreasonably withheld or delayed.

14.4.2. **Use of Name**. Except as set forth in Section 14.4.9, 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.

14.4.3. **Notice of Significant Events**. Each Party will notify (no later than three (3) Business Days after the information or results are obtained) the other Party of any significant event related to a Product (including any data, serious adverse event or regulatory advice or approval) so that the Parties may analyze the need to or desirability of publicly disclosing or reporting such event. Notwithstanding Section 14.4.1 above, any press release or other similar public communication by either Party related to a Product's efficacy or safety data and/or results, will be submitted to the other Party for review and approval at least three (3) Business Days in advance of such proposed public disclosure, which approval will not be unreasonably withheld or delayed.

14.4.4. **Before Option Exercise**. Before Option exercise, Ionis will have the sole right, consistent with its practice with its other compounds and products, to issue press releases, publish, present or otherwise disclose the progress and results regarding IONIS-FB-L_{Rx} to the public; *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 IONIS-FB-L_{Rx}, (i) Ionis will submit such proposed communication to Roche for review at least two (2) Business Days in advance of such proposed public disclosure, (ii) Roche 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 Roche.

14.4.5. **After Option Exercise**. After Option exercise, Roche will have the sole right, consistent with its practice with its other compounds and products, to issue press releases, publish, present or otherwise disclose the progress and results regarding IONIS-FB-L_{Rx} to the public; *provided*, that with respect to any proposed press release or other similar public communication by Roche disclosing regulatory discussions, the efficacy or safety data or results related to the Products or Roche's sales projections, (i) Roche will submit such proposed communication to Ionis for review at least two (2) 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) Roche will in good faith consider any changes that are timely recommended by Ionis.

14.4.6. **Scientific or Clinical Presentations**. Regarding any proposed scientific publications related to results from any Clinical Studies regarding Products, the Parties agree to use Commercially Reasonable Efforts to control public scientific disclosures of such results to prevent any 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 JPC an early draft of all such publications or presentations, at least forty-five (45) days prior to submission for publication including to facilitate the publication of any summaries of Clinical Studies data and results as required on the clinical trial registry of each respective Party. Each Party will review such proposed publication to avoid the unauthorized disclosure of a Party's Confidential Information and to preserve the patentability of inventions arising from the Development Plan or IDCP. If, during such forty-five (45)-day period, the other Party informs such Party that its proposed publication contains Confidential Information of the other Party, then such Party will delete such Confidential Information from its proposed publication. In addition, if during such forty-five (45)-day period, the other Party informs such Party that its proposed publication discloses non-public inventions made by either Party in the course of the Development under this Agreement, or the public disclosure of such proposed publication may 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 sixty (60) days from the date of such Party's objection, to permit the timely first filing of patent application(s), or (ii) remove the identified disclosures prior to publication.

14.4.7. **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.

14.4.8. **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.

14.4.9. **Acknowledgment; Commercial Materials**. Each Party will acknowledge in any press release, public presentation, publication or commercial marketing materials regarding the Collaboration or a Product, the other Party's role in discovering and developing a 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., Ionis: Nasdaq: IONIS; Roche: SIX: RO, ROG; OTCQX: RHHBY). Ionis may include the Products (and identify Roche as its partner for the Product) in Ionis' drug pipeline. In addition, subject to Applicable Law, the words "Discovered and developed by Ionis Pharmaceuticals" will be included and reasonably visible in Product communications and branding, provided that Roche will have final decision-making authority regarding the applicability of any legal and regulatory requirements for such acknowledgement.

ARTICLE 15.
MISCELLANEOUS

15.1. Dispute Resolution.

15.1.1. Escalation. If any dispute occurs under this Agreement (other than a dispute regarding the construction, validity or enforcement of either Party's Patents, which disputes will be resolved pursuant to Section 15.2), either Party may request in writing that the dispute be referred for resolution to the Head of Roche Partnering of Roche and the Chief Operating Officer of Ionis (the "***Executives***"). Within thirty (30) days after such a request, 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 the dispute. Each Party's JSC representatives may participate in such meeting if desired. If the Executives fail to resolve the dispute within such thirty (30)-day period, then, except as set forth in Section 4.1.1(b)(ii), the dispute will be referred to binding arbitration under Section 15.1.2.

15.1.2. Binding Arbitration. If a dispute subject to Section 15.1.1 is not resolved pursuant to Section 15.1.1, such dispute will be resolved through binding arbitration in accordance with this Section 15.1.2 and under the Commercial Arbitration Rules of the American Arbitration Association ("***AAA***") then in effect, including application of the "*Expedited Procedures*" (sections E-1, et al) of the Commercial Arbitration Rules of the AAA. The proceedings and decisions of the arbitrators will be confidential, final and binding on the Parties, and judgment upon the award of such arbitrators may be entered in any court having jurisdiction thereof. The arbitration will take place in Boston, Massachusetts, U.S. and will be conducted by three arbitrators. Each of Roche and Ionis will appoint one (1) arbitrator within thirty (30) days after the notice that initiated the arbitration. These two (2) arbitrators will in turn appoint a third arbitrator who will be reasonably acceptable to the Parties and who will be appointed in accordance with AAA rules. Each arbitrator chosen hereunder will have educational training and industry experience sufficient to demonstrate a reasonable level of scientific, financial, medical and industry knowledge relevant to the particular dispute.

15.2. Governing Law; Jurisdiction; Venue; Service of Process.

15.2.1. This Agreement and any dispute will be governed by and construed and enforced in accordance with the laws of the State of California, U.S., without reference to conflicts of laws principles.

15.2.2. Each Party hereby agrees that service of process: (a) made in any manner permitted by California law, or (b) made by overnight express courier service (signature required), prepaid, at its address specified pursuant to Section 15.7, 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.

15.3. **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 may 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 12.1 or Section 12.2). Except for the offsets and credits explicitly set forth in Section 9.10.3(b) and Section 9.12, 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.

15.4. **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, 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 a Party transfers or assigns this Agreement to [***] described in this Agreement, then such transferring Party (or such Affiliate) ("***Transferring Party***"), will [***] that the Transferring Party is obligated to pay to the non-transferring Party ("***Non-Transferring Party***") under ARTICLE 9 for the taxes withheld such that the Non-Transferring Party receives [***] assignment. In addition, Ionis may assign or transfer its rights to receive payments under this Agreement (but no liabilities), without Roche'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 15.4 will be null and void.

To the extent the Non-Transferring Party utilizes a [***] in any year, the Non-Transferring Party will [***] to the Transferring Party [***]. To assist the Transferring Party in determining when [***] pursuant to the foregoing sentence, beginning with the first Annual tax return for the year in which the [***] payment under this Section 15.4, and each year thereafter (including, for clarity, all years in which the Non-Transferring Party utilizes a [***], the Non-Transferring Party will provide the Transferring Party with the Non-Transferring Party's Annual tax returns (federal and state) and, in years in which the Non-Transferring Party utilizes the [***], supporting documentation for such [***].

15.5. **Change of Control**. If Ionis undergoes a Change of Control, then Roche will have the right at any time after it exercises the Option to disband the JSC and make unilateral decisions with respect to the Development Plan, IDCP, Development and Commercialization with no obligation to seek input from Ionis or its successor, if applicable.

15.6. **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 ninety (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.

15.7. **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: [***]

with a copy to:
Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Email: [***]

If to Roche, addressed to:
F. Hoffmann-La Roche Ltd
Grenzacherstrasse 124
4070 Basel, Switzerland
Attention: Corporate Legal Department
Fax: [***]

If to Roche, addressed to:
Hoffmann-La Roche Inc.
150 Clove Road, Suite 8
Little Falls, NJ 07424
Attention: Corporate Secretary
Fax: [***]

with a copy to: F. Hoffmann-La Roche Ltd
GRENZACHERSTRASSE 124
4070 BASEL, SWITZERLAND
ATTENTION: ALLIANCE MANAGER
FAX: [***]

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.

15.8. **Invoices**. All invoices that are required or permitted hereunder will be in writing and sent by Ionis to Roche at the following address or any other address that Roche may later provide:

F. Hoffmann-La Roche AG
Kreditorenbuchhaltung
4070 Basel
Switzerland

with an electronic copy to Roche's Alliance Manager.

Upon Ionis' request, Roche's Alliance Manager will provide Ionis' Alliance Manager with any additional information reasonably requested by Ionis to facilitate the prompt delivery of invoices to Roche, including a facsimile number for sending invoices.

15.9. **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.

15.10. **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.

15.11. **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.

15.12. **Entire Agreement**. This Agreement, together with the Schedules and Appendices hereto, sets forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties regarding the subject matter hereof and supersedes and terminates all prior agreements and understandings between the Parties pertaining to the subject matter hereof. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties regarding the subject matter hereof other than as set forth in this Agreement and the Schedules and Appendices hereto. 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.

15.13. **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.

15.14. **Interpretation**. Except as otherwise explicitly specified to the contrary, (a) references to a section, appendix or schedule means a section of, or appendix or schedule to this Agreement, unless another agreement is specified, (b) the word "*including*" (in its various forms) means "*including without limitation*", (c) 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, (d) words in the singular or plural form include the plural and singular form, respectively, (e) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement, (f) unless otherwise specified, "$" is in reference to United States Dollars, and (g) the headings contained in this Agreement, in any appendix 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.

15.15. **Further Actions**. Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate to carry out the expressly stated purposes and the clear intent of this Agreement.

15.16. **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.

15.17. **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.

15.18. **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.

[SIGNATURE PAGES FOLLOW]

* - * - * - *

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

F. HOFFMANN-LA ROCHE LTD

By: */s/ Stefan Arnold*
Name: Stefan Arnold
Title: Head Legal Pharma

By: */s/ Vikas Kabra*
Name: Vikas Kabra
Title: Head of Transaction Excellence

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their representatives thereunto duly authorized as of the Effective Date.

HOFFMANN-LA ROCHE INC.

By: */s/ John Parise*
Name: John Parise
Title: Authorized Signatory

SIGNATURE PAGE TO FB 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 Effective Date.

IONIS PHARMACEUTICALS, INC.

By: */s/ Stanley T. Crooke*
Name: Stanley T. Crooke
Title: Chief Executive Officer

SIGNATURE PAGE TO FB DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

LIST OF APPENDICES AND SCHEDULES

APPENDIX 1 – Definitions

APPENDIX 2 – Specific Performance Milestone Events

APPENDIX 3 – Permitted Licenses as of the Effective Date

SCHEDULE 4.2 – Alliance Management Activities

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SCHEDULE 9.7.2(e) – Royalty Calculation Examples

SCHEDULE 9.7.2(f) – Allocation of Net Sales

SCHEDULE 11.2.4(a) – Ionis Core Technology Patents

SCHEDULE 11.2.4(b) – Ionis Manufacturing and Analytical Patents

SCHEDULE 11.2.4(c) – Ionis Product-Specific Patents

SCHEDULE 11.2.6 – Prior Agreement

SCHEDULE 13.4.2(i) – Transition Activities

APPENDIX 1

DEFINITIONS

For purposes of this Agreement, the following capitalized terms will have the following meanings:

"***AAA***" has the meaning set forth in Section 15.1.2.

"***Acceptance of Filing***" 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 of written notice of validation by the EMA of such MAA 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 of Filing will be determined upon the validation of such MAA by the applicable Regulatory Authority in a Major Market in Europe, and (c) in Japan, receipt of written notice of acceptance of filing of such JNDA from the Koseisho (i.e., the Japanese Ministry of Health and Welfare, or any successor agency thereto).

"***Additional Core IP***" has the meaning set forth in Section 9.10.3(a).

"***Additional Ionis In-License Agreements***" has the meaning set forth in Section 9.10.1(a).

"***Additional Product-Specific Patents***" has the meaning set forth in Section 9.10.2(a).

"***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, more than fifty percent (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. Anything to the contrary in this paragraph notwithstanding, Chugai Pharmaceutical Co., Ltd, a Japanese corporation ("***Chugai***") and/or its subsidiaries (if any) and Foundation Medicine, Inc., a Delaware corporation ("***FMI***") and/or its subsidiaries (if any), will not be deemed an Affiliate of Roche unless Roche provides written notice to Ionis of its desire to include Chugai and/or FMI as an Affiliate of Roche.

"***Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***Agreement Term***" has the meaning set forth in Section 13.1.

"***Alliance Manager***" has the meaning set forth in Section 4.2.

"***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 (unless expressly stated otherwise) for a Product.

"***Applicable Law***" or "***Law***" means all applicable laws, statutes, rules, regulations and other pronouncements having the effect of law of any federal, national, multinational, state, provincial, county, city or other political subdivision, agency or other body, domestic or foreign, including any applicable rules, regulations, guidelines, or other requirements of the Regulatory Authorities that may be in effect from time to time.

"***Approval***" means (i) with respect to a Product in the EU, the earlier to occur of (A) approval from the applicable Regulatory Authority in at least one member state in the EU sufficient for the manufacture, distribution, use, marketing and sale of such Product, including pricing and reimbursement approval, in such jurisdiction in accordance with Applicable Laws, or (B) the First Commercial Sale of a Product in the EU or in a European country in a Major Market; and (ii) with respect to a Product in any regulatory jurisdiction other than the EU, approval sufficient for the manufacture, distribution, use, marketing and sale of such Product in such jurisdiction in accordance with Applicable Laws.

"***Approved Change***" has the meaning set forth in Section 3.1.5.

"***Approved Change Costs***" has the meaning set forth in Section 3.1.5.

"***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.

"***Audit Report***" has the meaning set forth in Section 9.12.

"***Bankruptcy Code***" has the meaning set forth in Section 13.2.5(b).

"***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 both New York, New York and Zurich, Switzerland are open for business.

"***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 2018, the Effective Date) and ending on December 31.

"***CDA***" has the meaning set forth in Section 14.2.

"***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 a Party: (a) the acquisition by any Third Party of beneficial ownership of more than fifty percent (50%) of the then outstanding common shares or voting power of such Party, other than acquisitions by employee benefit plans sponsored or maintained by such Party; (b) the consummation of a business combination involving such Party, unless, following such business combination, the stockholders of such Party immediately prior to such business combination beneficially own directly or indirectly more than fifty percent (50%) of the then outstanding common shares or voting power of the entity resulting from such business combination.

"***Chugai***" has the meaning set forth in the definition of Affiliate.

"***Claims***" has the meaning set forth in Section 12.1.

"***Clinical Study***" or "***Clinical Studies***" means a Phase 1 Trial, Phase 2 Trial, Registration-Directed 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, JNDA or other similar marketing application.

"***CMO***" means a Third Party contract manufacturer Manufacturing API or finished drug Product for any purpose under this Agreement.

"***Collaboration***" means the conduct of the Development Plan in accordance with this Agreement.

"***Collaboration Intellectual Property***" means collectively Ionis Collaboration Intellectual Property and Roche Collaboration Intellectual Property.

"***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 a Product in the applicable country, including conducting pre-and post-Approval activities, including studies reasonably required to increase the market potential of a Product and studies to provide improved formulation and Product delivery, and launching and promoting a Product in each country.

"***Commercializing Party***" means (a) Roche, with respect to a Product that is being Developed and Commercialized by or on behalf of Roche, 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, 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, (A) Commercially Reasonable Efforts as it applies to Roche's Development or Commercialization of a Product hereunder includes the use of Commercially Reasonable Efforts to (i) perform the activities assigned to Roche set forth in the Development Plan or IDCP in accordance with the timelines set forth therein, (ii) perform the "General Activities" set forth in Appendix 2, and (iii) achieve the specific performance milestone events set forth in Appendix 2 ("***Specific Performance Milestone Events***") for a Product on the timeline set forth in Appendix 2; and (B) Commercially Reasonable Efforts as it applies to Ionis' Development of IONIS-FB-L_{Rx} hereunder includes use of Commercially Reasonable Efforts to perform the activities assigned to Ionis under the Development Plan in accordance with the timelines set forth therein and the Specific Performance Milestone Events set forth in Appendix 2; provided, however, in each case, if regulatory or Development issues arise that are outside of either Party's reasonable control and make achievement of any Specific Performance Milestone Event on the stated timeline impossible, the Parties will meet and negotiate in good faith to revise, consistent with any applicable Additional Ionis In-License Agreements, the date by which the applicable Specific Performance Milestone Event must be achieved. However, Roche (and its Affiliates) does not always seek to market its own products in every country or seek to obtain regulatory approval in every country or for every potential Indication. As a result, the exercise of diligence by Roche is to be determined by judging Roche's commercially reasonable efforts in the Major Markets, taken as a whole.

"***Companion Diagnostic IP***" has the meaning set forth in Section 13.4.2(b).

"***Companion Diagnostic Product***" has the meaning set forth in Section 13.4.2(b).

"***Competitive Infringement***" has the meaning set forth in Section 10.5.1.

"***Complete***" 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 listing and tables of safety and efficacy data generated based on that primary database lock under the statistical analysis plan for such study are available.

"***Compound***" means an ASO that is designed to bind to the RNA that encodes Factor B where such ASO is discovered by Ionis prior to or in the performance of the Development Plan.

"***Compulsory Sublicense***" means a Sublicense granted to a Third Party, through the order, decree or grant of a governmental authority having competent jurisdiction, authorizing such Third Party to manufacture, use, sale, offer for sale, import or export a Product in any country.

"***Compulsory Sublicensee***" means a Third Party that was granted a Compulsory Sublicense.

"***Confidential Information***" has the meaning set forth in Section 14.1. "*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.

"***Conjugate Technology***" means a group of atoms covalently bound to an oligonucleotide designed to enhance one or more properties of the oligonucleotide, such as targeting of antisense drugs to specific tissues and cells. Conjugate Technology includes N-acetylgalactosamine (GalNAc) ligand conjugates capable of binding to the asialoglycoprotein receptor (ASGP-R) and enhancing the targeting of antisense drugs.

"***Control***", "***Controlled***" or "***Controlling***" 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 Roche Supported Pass-Through Costs in the case of Roche), 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 the act of making, using or selling by an unauthorized 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.

"***Develop***," "***Developing***" or "***Development***" means with respect to a Product, any and all discovery, characterization, or non-clinical (including non-clinical studies required to file an IND), clinical, or regulatory activity with respect to a Product to seek Approval (including the submission of all necessary filings with applicable Regulatory Authorities to support such non-clinical and clinical activities and Approval), including human clinical trials conducted after Approval of a Product to seek Approval for additional Indications for a Product.

"***Development Plan***" has the meaning set forth in Section 3.1.

"***Development Program*** has the meaning set forth in Section 3.1.

"***Disclosing Party***" has the meaning set forth in Section 14.1.

"***Discontinued Product***" means a Product that is the subject of a termination 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.

"***European Union***" or "***EU***" means each and every country or territory that is officially part of the European Union.

"***Executives***" has the meaning set forth in Section 15.1.1.

"***Existing Diagnostic Agreement***" means that certain Non-Exclusive G-Clamp License Agreement between Isis (now Ionis) and F. Hoffmann-La Roche Ltd dated April 26, 2011.

"***Factor B***" means the human gene complement factor B (GenBank accession # NM_001710; Gene ID: 629), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

"***FDA***" means the United States Food and Drug Administration and any successor entity thereto.

"***FDCA***" will mean the United States Food, Drug and Cosmetics Act.

"***Field***" means the prophylactic, therapeutic and diagnostic 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 of a Product by a Party under this Agreement.

"***First Commercial Sale***" means the first sale of a Product by Roche, its Affiliate or its Sublicensee to a Third Party in a particular country after Approval of a Product has been obtained in such country.

"***FMI***" has the meaning set forth in the definition of Affiliate.

"***FTE***" means a total of forty-seven (47) weeks or one thousand eight hundred eighty (1,880) hours per year of work on the Development of a Product carried out by employees of a Party having the appropriate relevant expertise to conduct such activities.

"***Full Royalty Period***" has the meaning set forth in Section 9.7.2(a).

"***Fully Absorbed Cost of Goods***" means the costs incurred by Ionis as determined using the methodology set forth in SCHEDULE 4.4.2 fairly applied and as employed on a consistent basis throughout Ionis' operations.

"***GA***" has the meaning set forth in ARTICLE 2.

"***Generic Product***" means, on a Product-by-Product and country-by-country basis, any product sold by a Third Party that is not a licensee or Sublicensee of Roche where such product(s) has the same active pharmaceutical ingredient as a Product and for which in the U.S. an ANDA has been filed naming such Product as the reference listed drug or outside of the U.S., an equivalent process where bioequivalence to such Product has been asserted, and such product(s) taken in the aggregate has a market share (measured in number of prescriptions during a Calendar Quarter with the numerator of such fractional share being the Generic Products taken in the aggregate, and the denominator being the total of the Generic Products taken in the aggregate plus the Product taken in the aggregate, as provided by IQVIA) in such country of at least [***].

"***Group Sublicensee***" means any individual, corporation, association or other business entity:

(i) to which Roche has granted a Sublicense;

(ii) that is not an Affiliate of Roche; and

(iii) that is consolidated within Roche's externally published audited financial statements.

"***gRED***" has the meaning set forth in Section 5.1.2.

"***HSR Act***" means Section 7A of the Clayton Act, as added by Title II of the Hart-Scott-Rodino Antitrust Improvement Act of 1976, as amended, and the rules and regulations promulgated thereunder.

"***IDCP***" has the meaning set forth in Section 8.1.1.

"***[***]***" has the meaning set forth in ARTICLE 2.

"***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.

"***Indemnitee***" has the meaning set forth in Section 12.3.

"***Indication***" means a primary sickness or medical condition or any interruption, cessation or disorder of a particular bodily function, system or organ (each a "disease") including sub-types and pediatric populations of the same disease. Indications that require separate pivotal trials to obtain Approval to market and sell a Product are separate Indications.

"***Initiation***" means, with respect to any Clinical Study, dosing of the first human subject in such Clinical Study.

"***Ionis***" has the meaning set forth in the Preamble of this Agreement.

"***Ionis Collaboration Know-How***" means Know-How discovered, developed, invented or created solely by or on behalf of Ionis or its Affiliate or a Third Party acting on their behalf in the performance of the Development Plan, that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Ionis Collaboration Patents***" means Patent Rights discovered, developed, invented or created solely by or on behalf of Ionis or its Affiliate or a Third Party acting on their behalf in the performance of the Development Plan, that are necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Ionis Collaboration Intellectual Property***" means Ionis Collaboration Know-How, Ionis Collaboration Patents and Ionis' interest in any Jointly-Owned Collaboration Intellectual Property.

"***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 or Conjugate Technology and not limited to a single specified gene target, other than Ionis Manufacturing and Analytical Patents. A list of Ionis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 11.2.4(a) attached hereto.

"***IONIS-FB-LRx***" means the compound known as ISIS 696844, which has the following structure: [***].

"***Ionis' Fully Absorbed Cost of Goods***" means the costs incurred by Ionis as determined using the methodology set forth in SCHEDULE 4.4.2 fairly applied and as employed on a consistent basis throughout Ionis' operations.

"***Ionis Internal ASO Safety Database***" has the meaning set forth in Section 8.2.2(a).

"***Ionis Know-How***" means any Know-How, including Ionis' interest in any Jointly-Owned Collaboration 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 Ionis' interest in any Jointly-Owned Collaboration 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 Ionis' interest in any Jointly-Owned Collaboration 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 of the Effective Date is set forth on SCHEDULE 11.2.4(b) attached hereto. Ionis Manufacturing and Analytical Patents do not include the Ionis Product-Specific Patents or the Ionis Core Technology Patents.

"***Ionis Product Reverse Royalties***" has the meaning set forth in Section 9.9.

"***Ionis Product-Specific Patents***" means Product-Specific Patents 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 11.2.4(c) attached hereto.

"***Ionis Supported Pass-Through Costs***" means the licensing costs and payments payable by Ionis to Third Parties to the extent arising from a Third Party agreement under [***] or [***].

"***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 Development Committee***" or "***JDC***" has the meaning set forth in Section 4.1.2.

"***Joint Patent Committee***" or "***JPC***" has the meaning set forth in Section 10.1.3(a).

"***Joint Steering Committee***" or "***JSC***" has the meaning set forth in Section 4.1.1.

"***Jointly-Owned Collaboration Know-How***" means Know-How discovered, developed, invented or created jointly in the performance of the Development Plan by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Jointly-Owned Collaboration Patents***" means any Patent Rights discovered, developed, invented or created jointly in the performance of the Development Plan by or on behalf of both Parties or their respective Affiliates or Third Parties acting on their behalf that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Jointly-Owned Collaboration Intellectual Property***" means Jointly-Owned Collaboration Know-How and Jointly-Owned Collaboration Patents.

"***Key Meeting***" has the meaning set forth in Section 8.1.6.

"***Know-How***" means unpatented 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.

"***Lead Party***" has the meaning set forth in Section 10.4.1.

"***Licensed CMO***" has the meaning set forth in Section 7.1.4(a)(ii).

"***Licensed Know-How***" means Ionis Manufacturing and Analytical Know-How, Ionis Know-How, Ionis Collaboration Know-How, and Ionis' interest in any Jointly-Owned Collaboration Know-How. For clarity, Licensed Know-How does not include any Know-How generated after the Effective Date covering formulation technology or delivery devices (other than any Conjugate Technology comprised in IONIS-FB-L_{Rx}) unless such Know-How is included in any Ionis Collaboration Know-How or Jointly-Owned Collaboration Know-How.

"***Licensed Patents***" means the Ionis Product-Specific Patents, Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents, Ionis Collaboration Patents, and Ionis' interest in any Jointly-Owned Collaboration Patents. For clarity, Licensed Patents do not include any Patent Rights filed after the Effective Date claiming formulation technology or delivery devices (other than any Conjugate Technology comprised in IONIS-FB-L_{Rx}) *unless* such Patent Rights are included in any Ionis Collaboration Patents or Jointly-Owned Collaboration Patents.

"***Licensed Intellectual Property***" means any and all Licensed Patents and Licensed Know-How, in each case to the extent necessary or useful to Develop, Manufacture or Commercialize a Product.

"***Losses***" has the meaning set forth in Section 12.1.

"***MAA***" means a marketing authorization application filed with the EMA 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.

"***MAA Approval***" means the Approval of an MAA by (i) the EMA for a Product in any country in the EU, or (ii) a Regulatory Authority for a Product in a European country that is a Major Market.

"***Major Market***" means any of the following countries: the United States, Japan, the United Kingdom, Germany, France, Italy, Spain, Brazil, Russia, India and China.

"***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 non-clinical, clinical, or commercial purposes, of API, Finished Drug Product or a Product.

"***Milestone Event***" means a Post-Licensing Milestone Event or a Sales Milestone Event, as applicable.

"***Minimum Third Party Payments***" means [***].

"***NDA***" means a New Drug Application filed with the FDA after completion of Clinical Studies to obtain Approval for a Product in the United States.

"***NDA Approval***" means the Approval of an NDA by the FDA for a Product in the U.S.

"***Net Sales***" of a Product in a particular period will mean the amount calculated by subtracting from the Sales of such Product for such period: (A) a lump sum deduction of four percent (4%) of Sales under item (i) of the "*Sales*" definition in lieu of those deductions that are not accounted for on a Product-by-Product basis (e.g., freight, postage charges, transportation insurance, packing materials for dispatch of goods, custom duties); (B) uncollectible amounts accrued during such period based on a proportional allocation of the total bad debts accrued during such period; (C) credit card charges (including processing fees) accrued during such period on such Sales; and (D) government mandated fees and taxes and other government charges accrued during such period for such Product including, for example, any fees, taxes or other charges that become due in connection with any healthcare reform, change in government pricing or discounting schemes, or other action of a government or regulatory body; provided that the foregoing deductions under (A) to (D) were not already taken as a gross-to-net deduction in accordance with the then currently used International Financial Reporting Standards (IFRS) in the calculation of Sales of such Product for such period.

"***New Third Party Licenses***" has the meaning set forth in Section 11.3.2.

"***Non-Breaching Party***" means the Party that believes the Breaching Party is in material breach of this Agreement.

"***Non-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 a Product and whether a Product has a desired effect.

"***Non-Rare Disease Indication***" means an Indication that is not a Rare Disease Indication.

"***Non-Transferring Party***" has the meaning set forth in Section 15.4.

"***Option***" has the meaning set forth in Section 6.1.

"***Option Deadline***" has the meaning set forth in Section 6.1.

"***Option Period***" has the meaning set forth in ARTICLE 2.

"***Party***" or "***Parties***" means Roche 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 non-clinical research, or (b) enable such Third Party to manufacture or formulate oligonucleotides, where 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 noncommercial research. A list of Permitted Licenses as of the Effective Date is set forth on APPENDIX 3 attached hereto.

"***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 the initial clinical testing of a Product in humans (first in humans study) in any country that is designed to satisfy the requirements of 21 C.F.R. § 312.21(a) FDCA, as amended from time to time, or a foreign equivalent thereof.

"***Phase 2 GA Trial***" means the Phase 2 Trial of IONIS-FB-L_{Rx} in GA commenced by Ionis and to be conducted in accordance with the Development Plan.

"***Phase 2 [***] Trial***" means the anticipated phase 2a trial of IONIS-FB-L_{Rx} in [***] to be conducted by Ionis in accordance with the Development Plan.

"***Phase 2b [***] Trial***" has the meaning set forth in Section 3.1.3.

"***Phase 2 Trial***" means a human clinical study of a Product that is intended to explore a variety of dose and dose response to generate initial evidence of clinical safety and activity in a target patient population for which the primary endpoints include a determination of dose ranges and/or a preliminary determination of efficacy in patients being studied as described in 21 C.F.R. § 312.21(b) FDCA, as amended from time to time, or a foreign equivalent thereof.

"***Phase 2 Trial Data Package***" means, with respect to the Phase 2 GA Trial and the Phase 2 [***] Trial, the listing and tables of safety and efficacy data available to Ionis after the last patient has received his/her last dose of a Product in each such trial. If, as of the time the Phase 2 Trial Data Package is complete, there is available to Ionis additional Phase 2 Trial data or any additional earlier stage Clinical Study data for the Product pursuant to Section 3.1.3, then Ionis will provide such additional data to Roche along with the Phase 2 Trial Data Package.

"***Phase 4 Trial***" means (i) any Clinical Study conducted to satisfy a requirement of a Regulatory Authority in order to maintain Approval for a Product, or (ii) any Clinical Study conducted after the first Approval in the same disease state for which a Product received Approval other than for purposes of obtaining Approval for such Product.

"***Post-Licensing Milestone Event***" has the meaning set forth in Section 9.4.

"***Post-Licensing Milestone Payment***" has the meaning set forth in Section 9.4.

"***Pre-Option Development Milestone Event***" has the meaning set forth in Section 9.2.

"***Pre-Option Development Milestone Payment***" has the meaning set forth in Section 9.2.

"***Prior Agreement***" means the agreement listed on SCHEDULE 11.2.6 attached hereto.

"***Proceeding***" means an action, suit or proceeding.

"***Product***" means any product, including any combination product, containing IONIS-FB-L_{Rx} as an active pharmaceutical ingredient regardless of its finished form, formulation or dosage.

"***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 claiming (i) the specific composition of matter of such Product, or (ii) methods of using such Product as a prophylactic or therapeutic, in each case to the extent necessary to Develop, Manufacture or Commercialize a Product; *provided however*, Patent Rights Controlled by Ionis or any of its Affiliates that (a) include claims that are directed to subject matter applicable to ASOs or products in general, or (b) include an ASO, the sequence of which targets the RNA that encodes Factor B and ASOs that do not target the RNA encoding Factor B, will not be considered Product-Specific Patents, and in the case of (a) and (b), such Patent Rights will be considered Ionis Core Technology Patents.

"***Proposed Phase 2 Trials***" means the Phase 2 GA Trial and the Phase 2 [***] Trial.

"***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.

"***Rare Disease Indication***" means an Indication for which the expected U.S. patient population with a disease eligible for treatment by the Product is two hundred thousand (200,000) or less as determined by the FDA Office of Orphan Products Development.

"***Receiving Party***" has the meaning set forth in Section 14.1.

"***Reduced Royalty Period***" has the meaning set forth in Section 9.7.2(d).

"***[***]***" has the meaning set forth in Section 9.7.2(b).

"***Registration-Directed Trial***" means a pivotal Clinical Study (whether or not called a "*Phase 3*" Clinical Study) [***] intended to establish that a Product is safe and effective for its intended use; and is intended to support NDA filing (or foreign equivalent filing) of such Product in patients having the disease or condition being studied, as described in 21 C.F.R. § 312.21(c) FDCA, as amended from time to time, or a foreign equivalent thereof.

"***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 regulatory applications, submissions, notifications, communications, correspondence, registrations, Approvals and/or other filings made to, received from or otherwise conducted with a Regulatory Authority that are necessary in order to Develop, Manufacture, obtain marketing authorization, market, sell or otherwise Commercialize a Product in a particular country or regulatory jurisdiction. Regulatory Materials include INDs, NDAs, MAAs, JNDAs, drug master files, presentations, responses, and applications for other Approvals. For clarity, Regulatory Materials also include written minutes of any meeting with any Regulatory Authorities, including minutes prepared by said Regulatory Authorities and those prepared by a Party's personnel.

"***Roche***" has the meaning set forth in the Preamble of this Agreement.

"***Roche Basel***" has the meaning set forth in the Preamble of this Agreement.

"***Roche Collaboration Know-How***" means Know-How discovered, developed, invented or created solely by or on behalf of Roche or its Affiliate or a Third Party acting on their behalf in the performance of the Development Plan or the IDCP, that is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Roche Collaboration Patents***" means Patent Rights discovered, developed, invented or created solely by or on behalf of Roche or its Affiliate or a Third Party acting on their behalf in the performance of the Development Plan or the IDCP, that are necessary or useful to Develop, Manufacture or Commercialize a Product in the Field.

"***Roche Collaboration Intellectual Property***" means Roche Collaboration Know-How, Roche Collaboration Patents and Roche's interest in any Jointly-Owned Collaboration Intellectual Property.

"***Roche Full Royalty***" has the meaning set forth in Section 9.7.1.

"***Roche Know-How***" means any Know-How that (i) did not arise in connection with the performance of the Development Plan, (ii) is owned, used, developed by, or licensed to Roche or its Affiliates, and (iii) is necessary or useful to Develop, Manufacture or Commercialize a Product in the Field, in each case to the extent Controlled by Roche or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***Roche US***" has the meaning set forth in the Preamble of this Agreement.

"***Roche Patents***" means any Patent Rights that (i) did not arise in connection with the performance of the Development Plan or IDCP, (ii) are owned, used, developed by, or licensed to Roche or its Affiliates, and (iii) are necessary or useful to Develop, Manufacture or Commercialize a Product in the Field, in each case to the extent Controlled by Roche or its Affiliates on the Effective Date or at any time during the Agreement Term.

"***Roche-Prosecuted Patents***" has the meaning set forth in Section 10.2.4(b).

"***Roche Reduced Royalty***" has the meaning set forth in Section 9.7.2(b).

"***Roche Supported Pass-Through Costs***" means [***].

"***Roche Intellectual Property***" means Roche's interest in Roche Collaboration Intellectual Property, Roche Know-How, Roche Patents and any trademarks described in Section 7.1.7, owned, used, developed by, or licensed to Roche or its Affiliates that is necessary or useful to Develop, Manufacture or Commercialize a Product.

"***[***]***" has the meaning set forth in Section 9.7.2(b).

"***Sales***" of a Product in a particular period will mean the sum of (i) and (ii):

(i) the amount stated in Roche sales line of its externally published audited financial statements with respect to such Product for such period (excluding sales to any Sublicensee that are used for research or Development or re-sold by such Sublicensee as sales under item (ii) below). This amount reflects the gross invoice price at which such Product was sold or otherwise disposed of (other than for use as clinical supplies or free samples) by Roche, its Affiliates and Group Sublicensees to Third Parties (excluding sales to any Sublicensee that are used for research or Development or re-sold by such Sublicensee as sales under item (ii) below) in such period reduced by gross-to-net deductions, if not previously deducted from such invoiced amount, taken in accordance with the then currently used International Financial Reporting Standards (IFRS).

By way of example, the gross-to-net deductions taken in accordance with International Financial Reporting Standards (IFRS) as of the Effective Date include the following:

(a) credits, reserves or allowances granted for (w) damaged, outdated, returned, rejected, withdrawn or recalled Product, (x) wastage replacement and short-shipments, (y) billing errors and (z) indigent patient and similar programs (e.g., price capitation);

(b) governmental price reductions and government mandated rebates;

(c) chargebacks, including those granted to wholesalers, buying groups and retailers;

(d) customer rebates, including cash sales incentives for prompt payment, cash and volume discounts; and

(e) taxes, duties and any other governmental charges or levies imposed upon or measured by the import, export, use, manufacture or sale of a Product (excluding income or franchise taxes).

For the purpose of clarity, sales by Roche and its Affiliates to any Sublicensee and/or Group Sublicensee that are used for research or Development or re-sold by such Sublicensee or Group Sublicensee as sales under item (ii) below will be excluded from "*Sales*" calculated under this item (i).

(ii) Sublicensee (excluding Compulsory Sublicensee) sales amounts reported to Roche and its Affiliates in accordance with Sublicensee contractual terms and their then currently used accounting standards. For the purpose of clarity, any Sublicensee sales as reported to Roche in accordance with Compulsory Sublicense agreements will be excluded from the Sales amount.

"***Sales Milestone Event***" has the meaning set forth in Section 9.5.

"***Sales Milestone Payment***" has the meaning set forth in Section 9.5.

"***Second Indication***" means either (i) any second Indication if the applicable Post-Licensing Milestone Event has already been achieved by a Non-Rare Disease Indication, or (ii) the first Rare Disease Indication for which the applicable Post-Licensing Milestone Event is achieved.

"***Specific Performance Milestone Event***" has the meaning set forth in the definition of "*Commercially Reasonable Efforts*".

"***Step-In Party***" has the meaning set forth in Section 10.4.1.

"***Sublicensee***" means a Third Party to whom a Party or its Affiliates or Sublicensees has granted a sublicense or license under any Licensed Intellectual Property or Roche Intellectual Property, as the case may be, licensed to such Party in accordance with the terms of this Agreement.

"***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 any Additional Ionis In-License Agreements) that relate to a Product, Factor B, including field or territory restrictions, covenants, milestone payments, diligence obligations, sublicense revenue, royalties, or other payments.

"***Transferring Party***" has the meaning set forth in Section 15.4.

"***Transition Activities***" has the meaning set forth in Section 13.4.2(*i*)(i).

"***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 (7) 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 and Commercialization Activities and Specific Performance Milestone Events

[***]

APPENDIX 3

Permitted Licenses as of the Effective Date

[***]

SCHEDULE 4.2

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 one hundred (100) days after the Effective Date to support the Development Plans;

(c) Organizing JSC and JDC meetings, including agendas, drafting minutes, and publishing final minutes;

(d) Supporting the co-chairs of the JSC and 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 JSC and JDC;

(f) Ensuring compliance in maintaining the Ionis Internal ASO Safety Database as outlined in Section 8.2.2(a); and

(g) Ensuring proper approval of publications prior to submission as required in Section 14.4.

SCHEDULE 4.4.2

Ionis' Fully Absorbed Cost of Goods Methodology
Cost Estimate of API Cost per Kilogram

[***]

SCHEDULE 9.7.2(e)

Royalty Calculation Examples

[***]

SCHEDULE 9.7.2(f)

Allocation of Net Sales

[***]

SCHEDULE 11.2.4(a)

Ionis Core Technology Patents

[***]

SCHEDULE 11.2.4(b)

Ionis Manufacturing and Analytical Patents

[***]

SCHEDULE 11.2.4(c)

Ionis Product-Specific Patents

[***]

SCHEDULE 11.2.6

Prior Agreement

[***]

SCHEDULE 13.4.2(i)

Transition Activities

Roche will perform Transition Activities, to the extent applicable at the time of the applicable termination, that are necessary to (1) provide patients with continued access to the applicable Products, (2) enable Ionis (or Ionis' designee) to assume and execute the responsibilities under all Approvals and then-ongoing Clinical Studies for the applicable Product, and (3) ensure long-term continuity of supply for the Product. Roche will perform the Transition Activities for Ionis through an agreed-upon schedule as set forth in an agreed upon transition plan, including but not limited in the following areas:

[***]

EXECUTION COPY

EXHIBIT 10.68

SECOND AMENDED AND RESTATED
STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

BETWEEN

IONIS PHARMACEUTICALS, INC.

AND

BIOGEN MA INC.

Dated October 17, 2018

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SECOND AMENDED AND RESTATED STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT

This SECOND AMENDED AND RESTATED STRATEGIC NEUROLOGY DRUG DISCOVERY AND DEVELOPMENT COLLABORATION, OPTION AND LICENSE AGREEMENT (the "***Agreement***") is entered into as of the 17th day of October, 2018 (the "***Second 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 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, 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 entered into 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 subsequently entered into an Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement (the "***First Amended and Restated Agreement***") dated October 20, 2017 (the "***First Amendment Date***"); and

WHEREAS, Biogen and Ionis seek to amend and restate the First Amended and Restated 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 (a) Compounds and Collaboration Products under such Collaboration Programs, (b) Biogen Alternate Modality Products or (c) 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 (a) the activities to support Target Sanction in the Calendar Year covered by such Neurological Disease Research Plan, (b) any Neurological Disease research to support Collaboration Programs, and (c) 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, unless either of such programs is terminated earlier by the Parties by written agreement (the "***Research Term***"); *provided, however*, that with respect to the Neurological Disease Research Program, (a) Ionis will not be required to begin target validation activities under the Neurological Disease Research Program (i) after the [***] anniversary of the Effective Date for any target that is not an ALS Target or (ii) after the [***] anniversary of the Effective Date for any ALS Target, in each case, unless otherwise agreed to by the Parties, and (b) if any target validation activities that are Ionis Activities are ongoing under the Neurological Disease Research Plan on such sixth anniversary, then Ionis will complete such activities in accordance with the Neurological Disease Research 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. As of the Second Amendment Date the Parties have completed all activities under the Core Research Program.

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 (i) [***], (ii) such gene target is not eligible to become a High Interest Target hereunder [***], or (iii) 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 until such Ionis Neurology Target is less 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 (1) 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, (2) [***] is not a Multi-Indication Target (as defined below) and (3) [***] 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 (a) [***] days following such meeting of the Neurology JRC or (b) [***] 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 (i) such High Interest Target (A) will not be designated a Collaboration Target or Biogen Alternate Modality Target and (B) will no longer be a Neurology Target under this Agreement and (ii) 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 (1) 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 (2) the provisions of clause (A) (but not clause (B)) 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 through June 7, 2018 (except, solely in the case of [***] and [***], through the end of 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 [***] 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 (or, with respect to clauses (a), (d) and (e) in this Section 1.9, the earlier termination of the Core Research Program), (a) neither Ionis nor Biogen will have an obligation to perform any activities under the Core Research Program or the Neurological Disease Research Program, (b) 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, (c) 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, (d) to the extent not previously provided to Ionis during prior meetings of the Neurology II JRC, at Ionis' reasonable 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 4.3.4 and (e) to the extent not previously provided to Biogen during prior meetings of the Neurology JRC, at Biogen's reasonable request, Ionis will provide to Biogen any data generated under the Core Research Program and the Neurological Disease Research Program and licensed to Biogen under Section 4.3.3. For clarity, the expiration of the Research Term will not affect Biogen's rights or Ionis' obligations with respect to 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 each Collaboration Program, Ionis will submit to 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, natural history studies or endpoint development 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, (iv) to the extent not previously provided to Ionis during prior meetings of the Neurology JRC, upon Ionis' request, Biogen will provide to Ionis any data generated under the Collaboration Program and licensed to Ionis under Section 4.3.4 and (v) to the extent not previously provided to Biogen during prior meetings of the Neurology JRC, upon Biogen's request, Ionis will provide to Biogen any data generated under the Collaboration Program and licensed to Biogen under Section 4.3.3. 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 First Amendment Date for the Collaboration Program for SOD-1. 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 the License Effective Date with respect to a Collaboration Program.

(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 after the License Effective Date with respect to a Collaboration Program, 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 (a) completion of the Initial Development Plans under all Collaboration Programs, which the Parties estimate will be approximately [***] years after the Effective Date, (b) exercise by Biogen of its Option for all Collaboration Programs, (c) the termination of the last Collaboration Program and (d) 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 (a) the Neurological Disease Research Program and progress toward achieving Target Sanction for each High Interest Target and progress related to ALS Targets, (b) activities conducted under the Core Research Program, (c) progress under each ASO Development Candidate Identification Plan toward designating a Development Candidate, (d) activities on the Deferred Targets conducted pursuant to Section 1.8.4 and (e) 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 the License Effective Date with respect to a Collaboration Program. 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 placed on the High Interest Target List or designated, as applicable, (a) 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 (b) so long as the other Party provides the Contracting Party such comments within [***] days after 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 the License Effective Date.

(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 the License Effective Date, 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 the License Effective Date**. After the License Effective Date 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 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 (A) 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 (B) 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 (1) this Section 1.14.1 will not be used to establish the initial milestone payments under Section 1.10.2(e), and (2) 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 (i) has an Estimated Biogen-Approved Cost of less than $[***] and (ii) 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 (i) has an Estimated Biogen-Approved Cost of $[***] or more and (ii) 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(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 (i) 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 (ii) 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 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 [***] 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 [***] 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 (including any amendments thereto that terminate all activities under such plans) 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 the License Effective Date with respect to the applicable Collaboration Program, (i) Ionis will have the final decision-making authority regarding [***] and (ii) Biogen will have the final decision-making authority regarding [***]. After the License Effective Date with respect to 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 the License Effective Date**. *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, (A) 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 (B) 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 (1) the provisions of ARTICLE 6 will apply with respect to such Biogen Alternate Modality Product, (2) 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, (3) 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 (4) 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 clause (d) of Appendix 3:

(a) The discovery, research, development, manufacture or commercialization of Gene-Editing Products or messenger RNA solely to the extent agreed by the Parties in writing;

(b) Any activities pursuant to the Prior Agreements as in effect on the Effective Date;

(c) The granting of, or performance of obligations under, Permitted Licenses;

(d) The research, development or commercialization of an Ionis Multi-Indication Compound to the extent permitted under Appendix 3;

(e) The exercise of its rights under Section 3.2.2;

(f) The discovery, research, development, manufacture or commercialization of a Pre-Existing Competitive Collaboration Product in accordance with Section 12.5.2(b) and Section 12.6; and

(g) The limited continuation of discovery, research, development, manufacture or commercialization of Acquired Competitive Product(s) as permitted under Section 12.5.3(a) and in accordance with Section 12.5.3(a) and Section 12.6.

2.1.3. **Limitations and Exceptions to Biogen's Exclusivity Covenants**. Notwithstanding anything to the contrary in this Agreement, Biogen's or its Affiliates' practice of the following will not violate Section 2.1.1 or clause (b) of Appendix 3:

(a) The discovery, research, development, manufacture or commercialization of Gene-Editing Products or messenger RNA solely to the extent agreed by the Parties in writing;

(b) the discovery, research, development, manufacture or commercialization of a Pre-Existing Competitive Collaboration Product in accordance with Section 12.5.2(b) and Section 12.6; or

(c) the limited continuation of discovery, research, development, manufacture or commercialization of Acquired Competitive Product(s) as permitted under Section 12.5.3(a) and in accordance with Section 12.5.3(a) and Section 12.6.

2.1.4. **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 the License Effective Date with respect to such Collaboration Program, 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 (a) Ionis' receipt of Biogen's notice electing to change a particular Collaboration Target to a Biogen Alternate Modality Target, and (b) 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 (i) 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 (ii) 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 (ii) 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 (ii) 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.

(a) **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(a), (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(a), 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).

(b) **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(b), (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 the License Effective Date 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 4.3.1(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 4.3.1(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 4.3.2 and any Sublicensee of Ionis under Section 4.5.2 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 4.4.2 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 the License Effective Date with respect to a particular Program. 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 Program 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 Program 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 Program, 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. Subject to the terms and conditions of this Agreement (including Ionis' exclusivity covenants under Section 2.1.1), 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 [***], (b) to conduct its activities with respect to such Program under the applicable ASO Development Candidate Identification Plans and applicable Initial Development Plans to the extent permitted by this Agreement, (c) to [***] with respect to such Program to the extent permitted by this Agreement, (d) to [***] to the extent permitted under APPENDIX 3 and (e) to exercise Ionis' rights under Section 2.1.1(f) (if applicable) or Section 3.2.2.

4.3. Enabling Licenses.

4.3.1. 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 4.3.2 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 (including the activities set forth on SCHEDULE 4.3.1(a)); *provided* that the grant of rights pursuant to this Section 4.3.1(a) shall not include the right to Manufacture any Compound or Product for Commercialization purposes.

(b) Subject to the terms and conditions of this Agreement (including Biogen's exclusivity covenants under Section 2.1.1), [***] for Biogen to conduct (i) Manufacturing of Compounds or Products under any Collaboration Program or (ii) any Biogen Activities that are Development activities with respect to any Collaboration Program in accordance with this Agreement, in each case ((i) and (ii) during the Option Period), 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 4.3.1(b) within [***] days after Biogen's receipt of the applicable invoice. For clarity, the grant of rights pursuant to this Section 4.3.1(b) shall not include the right to Commercialize any such Collaboration Product or to Manufacture any such Collaboration Product for Commercialization.

4.3.2. Biogen's Right to Sublicense. Biogen will have the right to grant sublicenses under the license granted under Section 4.3.1(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) [***] 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 after 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 4.3.2, which failure would cause an adverse effect on Ionis, then 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 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 to a Third Party pursuant to this Section 4.3.2 within [***] days after the execution thereof. For the avoidance of doubt, Section 4.1.3(b) shall apply to sublicenses granted under this Section 4.3.2.

4.3.3. Enabling Licenses to Biogen.

(a) 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, perpetual, worldwide, non-exclusive, sublicensable (subject to the restrictions set forth in Section 4.3.3(c)) 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 (i) a product that is being developed or commercialized by Biogen, its Affiliates or its Sublicensee under any Ionis/Biogen Additional Agreement or this Agreement, (ii) products that do not include an Oligonucleotide as an active pharmaceutical ingredient, and (iii) Gene-Editing Products. The licenses in clause (ii) and clause (iii) of this Section 4.3.3(a) and in Section 4.3.3(b) are royalty-free; *except* that if a product that is not a Product is being sold by Biogen, its Affiliates or Sublicensees is Covered by a Target Related Ionis Program Claim in a country, then on a country-by-country basis Biogen will pay to Ionis a royalty equal to [***]% of Net Sales of such 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 (A) is within an Ionis Program Patent that is solely owned by Ionis, (B) Covers a product being sold by Biogen, its Affiliates or Sublicensee and (C) claims a gene target, or a method of modulating such gene target to achieve a prophylactic or therapeutic effect/benefit.

(b) 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, perpetual, worldwide, non-exclusive, sublicensable (subject to the restrictions set forth in Section 4.3.3(c)) license under any Ionis Program Know-How and any Enabled Core Program Patents, in each case, Controlled by Ionis or its Affiliates at any time during the Agreement Term, to research, develop, manufacture, have manufactured and commercialize any product, including products that include an Oligonucleotide as an active pharmaceutical ingredient.

(c) Biogen may share any raw data included in the Ionis Program Know-How licensed to Biogen under Sections 4.3.3(a) and 4.3.3(b) for use in connection with the performance of its obligations or exercise of its rights under this Agreement or any Ionis/Biogen Additional Agreement, and Biogen may share the conclusions drawn from or based on the review of such raw data with any Third Party. Other than in accordance with the foregoing sentence, Biogen shall not share with any Third Party that is not an academic or non-profit institution or a contractor acting on Biogen's behalf any raw data included in such Ionis Program Know-How or any tangible embodiments thereof to the extent such raw data and tangible embodiments constitute Confidential Information of Ionis.

4.3.4. Enabling License to Ionis.

(a) Subject to the terms and conditions of this Agreement (including Ionis' exclusivity covenants under Section 2.1.1), Biogen hereby grants Ionis an irrevocable, perpetual, worldwide, non-exclusive, sublicensable (subject to the restrictions set forth in Section 4.3.4(c)) 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 4.4.1, 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 Ionis/Biogen Additional Agreement) and (b) Gene-Editing Products. The licenses set forth in this Section 4.3.4(a) and in Section 4.3.4(b) are royalty-free; *except* that if a product that is not a Discontinued Product being sold by Ionis, its Affiliates or Sublicensee is Covered by a Target Related Biogen Program Claim in a country, then on a country-by-country basis Ionis will pay to Biogen a royalty equal to [***]% of net sales of such 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 4.3.4. 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.

(b) Subject to the terms and conditions of this Agreement (including Ionis' exclusivity covenants under Section 2.1.1), Biogen hereby grants Ionis an irrevocable, perpetual, worldwide, non-exclusive, sublicensable (subject to the restrictions set forth in Section 4.3.4(c)) license under any Biogen Program Know-How and any Enabled Core Program Patents, in each case, Controlled by Biogen or its Affiliates at any time during the Agreement Term, to research, develop, manufacture, have manufactured and commercialize any product, including products that do not include an Oligonucleotide as an active pharmaceutical ingredient.

(c) Ionis may share any raw data included in the Biogen Program Know-How licensed to Ionis under Sections 4.3.4(a) and 4.3.4(b) for use in the performance of its obligations or exercise of its rights under this Agreement or any Ionis/Biogen Additional Agreement, and Ionis may share the conclusions drawn from or based on the review of such raw data with any Third Party. Other than in accordance with the foregoing sentence, Ionis shall not share with any Third Party that is not an academic or non-profit institution or a contractor acting on Biogen's behalf any raw data included in such Biogen Program Know-How or any tangible embodiments thereof to the extent such raw data and tangible embodiments constitute Confidential Information of Biogen.

4.4. Licenses to Ionis for Biogen Results.

4.4.1. 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 under this Agreement or the Ionis/Biogen Additional Agreements) and (b) Gene-Editing Products.

4.4.2. The license granted in Section 4.4.1 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 to 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 4.4.2 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 4.4 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 4.4.2.

4.5. Right to Obtain Direct License from Biogen to Ionis Partner; Sublicensees of Ionis.

4.5.1. If requested by Ionis, Biogen shall grant a direct, [***] license under the Biogen Results to [***] on the same terms as set forth in Section 4.4 with respect to sublicenses of Ionis. Biogen shall endeavor in good faith to grant such license within [***] days of any such request by Ionis.

4.5.2. Ionis will have the right to grant sublicenses under the licenses granted under Section 4.4, *provided* that each such sublicense will be subject to, and consistent with, the terms and conditions of this Agreement. If, within [***] days after 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 4.5.2, 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 4.5.2 within [***] days after the execution thereof.

4.6. 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.

4.7. Subcontracting.

4.7.1. Subject to the terms of this Section 4.7, 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.

4.7.2. Ionis agrees that, where Biogen wishes to (sub)contract with a Third Party with respect to any of the rights granted under Section 4.3.1(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 4.3.1(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 4.7.2 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 First 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.

4.8. **Technology Transfer**.

4.8.1. **Technology Transfer to Biogen during the Option Period**. Within [***] days after the First 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.

4.8.2. **Technology Transfer to Biogen after the License Effective Date**. On a Collaboration Program-by-Collaboration Program basis, Ionis will promptly, but no later than [***] after the License Effective Date with respect to a Collaboration Program, 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*, (i) 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 (A) any non-public data or information, in each case, related solely to the applicable Development Candidate, or (B) any Confidential Information of Biogen, and (ii) 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 (i) of the preceding sentence that are not in the public domain and do not relate to Ionis' antisense oligonucleotide chemistry 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 4.8.2(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 4.8.2(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 the License Effective Date with respect to such Collaboration Program, 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 4.8.2(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.

4.8.3. **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 4.3.3 and Section 4.3.4, 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 the License Effective Date with respect to a Collaboration Program, 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 the License Effective Date with respect to 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 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) after the License Effective Date for a Collaboration Program that is not an ALS Collaboration Program, and (ii) following the designation of the Development Candidate for an ALS Collaboration Program or a Biogen Conducted Non-ALS Collaboration Program, 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 the License Effective Date with respect to a Collaboration Program 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 the License Effective Date with respect to a Collaboration Program, 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 License Effective Date. 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 License Effective Date 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 First 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 the License Effective Date for a particular Collaboration Program, 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(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 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(c) 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(c) 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 interests in and to the Licensed Know-How and Licensed Patents and Biogen will own and retain all of its rights, title and interests 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 and will be 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 interests thereto, subject to any rights or licenses expressly granted by Biogen to Ionis under this Agreement. As between the Parties, Ionis is and will be 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 interests 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 and will be owned jointly by Biogen and Ionis on an equal and undivided basis, including all rights, title and interests 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***" promptly following the Effective Date. 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, with responsibilities including (i) the preparation of the intellectual property strategy to govern the Parties' activities set forth in the Neurological Disease Research Plan and the activities set forth in this ARTICLE 7, (ii) making recommendations following discussion by the Parties regarding Third Party intellectual property rights that may be necessary or useful to perform activities under, and the intellectual property considerations to be taken into account in, the Neurological Disease Research Plan, (iii) making recommendations with respect to intellectual property considerations to be taken into account in each ASO Development Candidate Identification Plan, (iv) the preparation of recommendations with respect to intellectual property considerations in connection with proposed Development Candidates for consideration by the Parties, (v) assessing and making recommendations to the Neurology JDC prior to the completion of IND-Enabling Toxicology Studies regarding any Patent Rights of any Third Party that may be necessary or useful for the Development, Manufacture or Commercialization of any Development Candidate that is the subject of such IND-Enabling Toxicology Studies and (vi) evaluating any activities under a Neurology Plan that are proposed to be conducted with an academic or non-profit collaborator and making recommendations as to where and with whom such activities should be conducted, and in each case will cooperate with respect to any such activities. Ionis' obligation to participate in the JPC will terminate on the later of (A) the end of the Research Term and (B) 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, but shall nevertheless continue to coordinate with Biogen with respect to the activities set forth in this ARTICLE 7 during the Agreement Term.

(b) The JPC will discuss a strategy and make recommendations with regard to intellectual property considerations (i) with respect to the Parties' activities under the Core Research Program and the Neurological Disease Research Program, promptly following the Second Amendment Date and (ii) with respect to each Collaboration Program, promptly after such Collaboration Program is designated, which strategies shall include (A) considerations for identifying potential inventions and making inventorship determinations, (B) considerations when selecting each Development Candidate, (C) considerations for 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, Biogen Product-Specific Patents and Jointly-Owned Program Patents, (D) defense against allegations of infringement of Third Party Patent Rights and (E) licenses to Third Party Patent Rights or Know-How, in each case ((A) through (E)) to the extent such matter would be reasonably likely to have a material impact on the Agreement or the ownership of intellectual property or the licenses granted hereunder. The applicable strategy and the JPC's recommendations, as applicable, will be considered in good faith in the performance of the Neurology Plans, the preparation of the intellectual property assessment to be included in each Development Candidate Data Package and 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.

(c) 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 or misappropriated (as applicable) by the Development, 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 Section 7.1.3(f)) determines that any Collaborator IP would be infringed or misappropriated (as applicable) by the Development, Manufacture or Commercialization of such Development Candidate or Compound, [***]; *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, then such Party shall use commercially reasonable efforts to obtain [***] 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.

(d) Notwithstanding any provision to the contrary in this Agreement, including under Section 6.11, 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 [***] as follows: (i) in the case where [***] enters into such Collaborator License, [***] will be solely responsible for paying any payment obligations that [***], except that [***] will be solely responsible for paying any payment obligations that [***] under any such Collaborator Licenses that [***] approved prior to execution thereof, and (ii) in the case where [***] enters into such Collaborator License, [***] will be [***] responsible for paying any payment obligations that [***].

(e) 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 the License Effective Date for the applicable Collaboration Program. If, Biogen timely provides Ionis with such a written notice to exclude certain of such Collaborator IP from such license, then such Collaborator IP will not be included in the Licensed Technology licensed with respect to such Collaboration Program under this Agreement. If Biogen does not provide Ionis with such a written notice to exclude such Collaborator IP prior to the License Effective Date for the applicable Collaboration Program hereunder, then 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 Collaboration Program under this Agreement.

(f) In case of a dispute in the Joint Patent Committee over whether any Collaborator IP would be infringed or misappropriated (as applicable) by the Development, 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.

(g) In addition, the Joint Patent Committee will be responsible for the determination of inventorship of Patent Rights that claim or cover Know-How discovered, developed, invented or created under this Agreement 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, then 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.

(h) 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 of its members 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**. Subject to Biogen's right to provide reasonable input and comment as set forth in Section 7.2.5(a), the Party responsible for Prosecution and Maintenance of any Patent Rights as set forth in Section 7.2.2 and Section 7.2.3 will endeavor to obtain patent protection for the applicable Product as it Prosecutes and Maintains its other patents Covering products in development, using counsel of its own choice but reasonably acceptable to the other Party, in such countries as the responsible Party sees fit.

7.2.2. **Licensed Patents and Biogen Patents**.

(a) **Licensed Patents In General**. Prior to the License Effective Date for a Collaboration Program or Biogen Alternate Modality Program (as applicable) (a "***Program***"), and subject to Biogen's right to provide reasonable input and comment as set forth in Section 7.2.5(a), 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 for such Program, subject to this Section 7.2.2(a) 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. Ionis will use commercially reasonable efforts to diligently Prosecute and Maintain all Jointly-Owned Program Patents for which Ionis has the right to Prosecute and Maintain. On a Program-by-Program, until the earlier of the License Effective Date with respect to such Program 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 that are the subject of such Program to the extent that Ionis has the right to Prosecute and Maintain such Patent Rights.

(b) **Licensed Patents After License Effective Date**. Upon the License Effective Date with respect to a Program, 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 subject to the license under Section 4.1.1 for such Program to the same extent Ionis had the right to control and was responsible for such Prosecution and Maintenance immediately prior to such License Effective Date, 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**. Subject to Biogen's right to provide reasonable input and comment as set forth in Section 7.2.5(a), 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 License Effective Date for a Program and subject to Biogen's right to provide reasonable input and comment as set forth in Section 7.2.5(a), 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 Program. After the License Effective Date for a Collaboration Program, 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 Program.

7.2.4. **Prosecution of Multi-Indication Product-Specific Patents; Biogen Supremacy to Enforce and Extend**. With respect to Product-Specific Patents 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 (a) a Multi-Indication Product licensed to Biogen under Section 4.1.1(a), and (b) 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), upon the grant of such license, 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) Ionis will keep Biogen reasonably informed through the Joint Patent Committee (or directly, if the Joint Patent Committee has been disbanded) as to material developments with respect to the Prosecution and Maintenance of (i) those Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents that Cover any Development Candidate or Product and (ii) the Ionis Product-Specific Patents and Jointly-Owned Program Patents, in each case ((i) and (ii)), for which Ionis has the responsibility to Prosecute and Maintain 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. Ionis will timely provide Biogen the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance, including the countries in which such Patent Rights are filed, and will consider Biogen's input with respect to such strategic aspects in good faith but which will not be binding on Ionis. Additionally, Ionis will promptly provide to Biogen drafts of all patent-related filings and communications related to the such Patent Rights, including copies of office actions or other correspondence that Ionis receives from any patent office, drafts of office action responses or other correspondence that Ionis provides to any patent office, and copies and drafts of all interferences, reissues, re-examinations, oppositions or requests for patent term extensions, in each case, for Biogen's review and comment, and Ionis will consider in good faith any reasonable comments timely provided by Biogen with respect to such draft filings and communications.

(b) Following the License Effective Date with respect to a particular Program, Biogen will keep Ionis reasonably informed through the Joint Patent Committee (or directly, if the Joint Patent Committee has been disbanded) as to material developments with respect to the Prosecution and Maintenance of Product-Specific Patents or Jointly-Owned Program Patents for which Biogen has the responsibility to Prosecute and Maintain 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 and will provide Ionis the timely opportunity to have reasonable input into the strategic aspects of such Prosecution and Maintenance, which input Biogen will consider in good faith but which will not be required to implement. Following the License Effective Date with respect to a particular Program, Biogen will have final decision-making authority with respect to the Prosecution and Maintenance, enforcement and defense of such Product-Specific Patents or Jointly-Owned Program Patents related to such Program, including any Proceeding related to the infringement of such Patent Rights and any patent term extensions related to such Patent Rights.

(c) If Biogen elects (i) not to file and prosecute patent applications for the Jointly-Owned Program Patents 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, (ii) not to continue the Prosecution and Maintenance (including any interferences, oppositions, reissue proceedings, re-examinations, and patent term extensions, adjustments, and restorations) of any Biogen-Prosecuted Patent in a particular country or (iii) 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 in each case ((i) – (iii)), Biogen will so notify Ionis promptly in writing of its intention (including a reasonably detailed rationale for doing so) with sufficient 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(d) 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, 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(c), then Ionis will have no obligation to notify Biogen if Ionis intends to abandon such Biogen-Prosecuted Patent.

(d) Notwithstanding Section 7.2.5(c) 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(c) above to file or prosecute the Conflicting Patent Right.

(e) If, during the Agreement Term, Ionis intends not to file or to abandon in any jurisdiction 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 and final decision-making authority 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(e), then Biogen will have no obligation to notify Ionis if Biogen intends to abandon such Ionis Product-Specific Patent.

(f) The Parties, through the Joint Patent Committee (or directly, if the Joint Patent Committee has been disbanded), 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, following which determination such a divisional or continuation filing will be made.

(g) If the Party responsible for Prosecution and Maintenance of a Jointly-Owned Program Patent 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 and final decision-making authority 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 interests 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(g), such Party will have no obligation to notify the other Party of any intention of such Party to abandon such Jointly-Owned Program Patents.

(h) In addition, the Parties will consult, through the Joint Patent Committee (or directly, if the Joint Patent Committee has been disbanded), 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 License Effective Date for a Program, Biogen will be solely responsible for Patent Costs arising from the Prosecution and Maintenance of the Ionis Product-Specific Patents related to such Program.

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 License Effective Date for the applicable Program 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 License Effective Date for the applicable Program 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. Notwithstanding the foregoing, (i) if Ionis is the Lead Party, then Ionis will cooperate in good faith with Biogen on the institution, prosecution and control of such Proceeding, will provide Biogen with copies of filings, submissions and communications related to such Proceeding in sufficient time to allow Biogen to review and comment thereon, and will incorporate any reasonable comments timely provided by Biogen with respect to such filings, submissions and communications and (ii) if Biogen is the Lead Party and Ionis is a named party, then Biogen will cooperate in good faith with Ionis on the institution, prosecution and control of such Proceeding and will provide Ionis the timely opportunity to have reasonable input into the strategic aspects of such Proceeding, which Biogen will consider in good faith but which will not be required to implement. 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, then 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 (a) the enforcement of the other Party's Know-How or Patent Rights (e.g., a counterclaim of infringement), or (b) 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 conflicting obligation of confidentiality with respect to any Licensed 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 7.5.8 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 License Effective Date for the Program of which such Product is the subject, 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. 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. Additionally, Ionis will provide Biogen with copies of filings, submissions and communications related to such Proceeding in sufficient time to allow Biogen to review and comment thereon, and will consider in good faith any reasonable comments timely provided by Biogen with respect to such filings, submissions and communications. Subject to the preceding sentence, Ionis will have the sole right to control such litigation. 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. Biogen Enforcement Rights. Notwithstanding Section 7.5.2 and Section 7.5.4, in the case where a Third Party is infringing an Ionis Core Technology Patent and a Patent Right Controlled by Biogen by reason of the development, manufacture, use or commercialization of a product directed against the RNA that encodes a High Interest Target, Collaboration Target in the Field, then such Party will promptly notify the other Party in writing. If Biogen also enforces any Patent Rights Controlled by Biogen (including any Ionis Product-Specific Patents assigned by Ionis to Biogen under this Agreement) against such infringement, then Biogen may elect to have Ionis and Biogen enforce the applicable Ionis Core Technology Patents and the applicable Patent Rights Controlled by Biogen against such infringing Third Party.

7.5.4. **Following License Grant**. For any Competitive Infringement with respect to a particular Product (except for a Discontinued Collaboration Product) occurring after the License Effective Date for the Program of which such Product is the subject, 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 7.5.4 to the extent involving any Ionis Core Technology Patents or Ionis Manufacturing and Analytical Patents.

7.5.5. **Joinder**.

(a) If a Party initiates a Proceeding in accordance with this Section 7.5, then 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 7.5.6, the costs and expenses of each Party incurred pursuant to this Section 7.5.5(a) will be borne by the Party initiating such Proceeding.

(b) If one Party initiates a Proceeding in accordance with this Section 7.5.5, then 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 or where such Proceeding relates to Jointly-Owned Program Patents.

7.5.6. **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 License Effective Date for the Program of which the applicable Product is the subject will be (i) [***]; or (ii) [***]; then

(c) any remaining proceeds constituting direct or actual damages for acts of infringement occurring after the License Effective Date for the Program of which the applicable Product is the subject [***]; 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.

7.5.7. **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.

7.5.8. **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: (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); (b) any remaining proceeds constituting direct damages will be [***], and (c) any remaining proceeds constituting punitive or treble damages will be allocated as follows: (i) if the Parties jointly initiate a Proceeding pursuant to this Section 7.6.1, [***]; and (ii) 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 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 (a) New Third Party License the restrictions and obligations of which Biogen has agreed to under Section 6.13.2, (b) Prior Agreements, and (c) 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 the Product. After the License Effective Date for the Collaboration Program of which such Product is the subject, 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 Second Amendment 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, to comply with the terms of Section 2.1 and will not permit any Affiliates to conduct any activities that Ionis is prohibited from conducting under 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 Competitive Product. If, after the acquisition by a Party of a Third Party that is developing or commercializing an Acquired Competitive Product or an Acquired Competitive Program, such Party does not, by the end of the Collaboration Divestiture Period, divest itself of a Competitive Collaboration Product or Competitive Collaboration Program, as applicable, or terminate the development and commercialization of such Acquired Competitive Product or activities under such Acquired Competitive Program or assign this Agreement to a Third Party that is not itself developing or commercializing a Competitive Collaboration Product or engaged in a Competitive Collaboration Program, as set forth in Section 12.5.3, then the non-acquiring Party may terminate this Agreement solely with respect to the Collaboration Program(s) affected thereby immediately upon providing written notice to the acquiring Party.

10.2.3. Termination Due to Failure to Obtain HSR Clearance.

(a) If the Parties make an HSR Filing with respect to a proposed 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 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 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 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 the applicable License Effective Date, 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 License Effective Date**. If, prior to the License Effective Date 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 4.8 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 4.8 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 4.3.3 (Enabling License to Biogen), Section 4.3.4 (Enabling License to Ionis), Section 4.4 (Licenses to Ionis for Biogen Results), Section 4.5 (Right to Obtain Direct License from Biogen to Ionis Partner; Sublicensees of Ionis), Section 4.8.2 (Technology Transfer after License Effective Date) (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 License Effective Date)), 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** Prior to License **Effective Date**. If this Agreement expires or is terminated by a Party in accordance with this ARTICLE 10 before the License Effective Date for a particular Program, 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 (i) 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 (ii) 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 the License Effective Date 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*, (A) 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 (other than any Gene-Editing Product or messenger RNA) as an active pharmaceutical ingredient, *provided, further* that, for such products that do not include such an Oligonucleotide as an active pharmaceutical ingredient, such excerpts or portions shall not include any Confidential Information of Ionis, and (B) 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 (A) 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 4.8, *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 (other than any Gene-Editing Product or messenger RNA) as an active pharmaceutical ingredient, *provided, further* that, for such products that do not include such 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 Effective Date**. If this Agreement is terminated by a Party in accordance with this ARTICLE 10 after the License Effective Date 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 4.8, *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 License Effective Date.

(a) **Termination of Committees and Information Sharing**. If, after the License Effective Date with respect to a particular Collaboration Program, 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 4.8 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 terms of this Section 10.4.6 shall apply.

(b) In such event, the Parties wish to provide a mechanism to ensure that patients who were being treated with the applicable Product prior to such termination or who desire access to such Product can continue to have access to such Product until the regulatory and commercial responsibilities for the Product are transitioned from Biogen to Ionis following the termination of the applicable Product. 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 (i) provide patients with continued access to the applicable Products, (ii) following the termination of this Agreement with respect to the applicable Product, transition the responsibilities under all Approvals and ongoing Clinical Studies for the applicable Product to Ionis or its designee and (iii) following termination of this Agreement with respect to the applicable Collaboration Target, 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(c), 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(b), Ionis shall not conduct activities with respect to any Discontinued Products to the extent prohibited by ARTICLE 2 of this Agreement.

(c) Ionis may elect to have Biogen perform the Transition Services by providing written notice to Biogen no later than the earlier of (i) [***] days following the effective date of the termination and (ii) [***] days following written notice by Biogen to Ionis asking Ionis to confirm if Ionis wishes to have Biogen perform the Transition Services (provided Biogen did not send such a notice earlier 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 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.

(d) 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.

(e) 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 the License Effective Date for such Collaboration Program, Ionis will have final decision-making authority regarding such matter, and (ii) after the License Effective Date for such Collaboration Program, 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, (a) Biogen will submit such proposed communication to Ionis for review at least two Business Days in advance of such proposed public disclosure, (b) Ionis will have the right to review and recommend changes to such communication and (c) 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 (i) whether such proposed public announcement, press release or other public disclosure shall be issued or made and (ii) 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 (a) 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 (b) remove the identified disclosures prior to publication. With respect to each Clinical Study, (i) 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 (ii) 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 ((i) and (ii)), 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 (A) 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, (B) 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 (C) 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 Programs 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 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 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 12.8, 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 of Ionis 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. **Pre-Existing Competitive Collaboration Programs of an Acquirer**. If, at any time during the Agreement Term, a Change of Control of a Party occurs involving a Person that, at the time of the execution of such Change of Control, is (A) developing or commercializing a (1) Competitive Product or (2) Competitive Indication Collaboration Product within the Field (such pre-existing Competitive Collaboration Products and Competitive Indication Products, each, a "***Pre-Existing Competitive Collaboration Product***") or (B) is engaged in a (1) Competitive Collaboration Program or (2) Competitive Indication Program (such pre-existing Competitive Collaboration Programs and Competitive Indication Collaboration Programs, each, a "***Pre-Existing Competitive Collaboration Program***," and such Person being hereinafter referred to as a "***Competing Collaboration Acquirer***"), then in each case ((A) and (B)):

(a) such Party shall promptly provide written notice to the other Party of such Change of Control;

(b) if such Change of Control involved Ionis, then Biogen may elect that some or all of the Biogen Reduced Participation and Information Obligations will apply to the Collaboration Programs to which the Pre-Existing Competitive Collaboration Product or Pre-Existing Competitive Collaboration Program relate;

(c) such Party shall conduct activities pursuant to Section 12.6 to separate its Development activities under this Agreement from its development activities relating to any Pre-Existing Collaboration Competitive Product(s) and Pre-Existing Competitive Collaboration Program(s);

(d) the research, development, manufacture or commercialization of any Pre-Existing Competitive Collaboration Product(s) by a Competing Collaboration Acquirer will not be a violation of such Party's exclusivity covenants under Section 2.1.1 and Section 12.5.3(a) will not apply to any such Pre-Existing Competitive Collaboration Product or Pre-Existing Competitive Collaboration Program; *provided* that the conditions of Section 12.5.2(a) and Section 12.5.2(c) are satisfied.

12.5.3. Acquired Competitive Programs; Acquired Associated Programs.

(a) If, at any time during the Agreement Term, either Party acquires a Third Party or a portion of the business of a Third Party (whether by merger, stock purchase or purchase of assets) that is, prior to such acquisition, engaged in discovering, researching, developing or commercializing a Competitive Collaboration Product within the Field or is engaged in a Competitive Collaboration Program, in each case that would violate the provisions of ARTICLE 2 if conducted by such Party (such acquired Competitive Collaboration Product an "***Acquired Competitive Product***" and such acquired Competitive Collaboration Program an "***Acquired Competitive Program***"), then the limited continuation of the research, development, manufacture or commercialization of the Acquired Competitive Product(s) or Acquired Competitive Programs by the acquiring Party as permitted in this Section 12.5.3(a) in a manner that would have been in the ordinary course of business of such Third Party will not be a violation of such acquiring Party's exclusivity covenants under Section 2.1.1, *provided that*, following the closing of such acquisition, the conditions set forth in Sections 12.5.3(a)(i) through 12.5.3(a)(iv) are met:

(i) Such acquiring Party shall promptly provide written notice to the other Party of such acquisition;

(ii) Such acquiring Party shall use reasonable efforts to divest all such Acquired Competitive Products and Acquired Competitive Programs promptly following the closing of such acquisition, and in any event such Party shall complete such divestment within [***] after the closing of such acquisition (the "***Collaboration Divestiture Period***"); provided that such Collaboration Divestiture Period shall be extended, and such Party shall not be in breach of this Section 12.5.3(a) if, at the expiration thereof (and any extensions thereto), such Party provides competent evidence of reasonable ongoing efforts to divest such Acquired Competitive Products and Acquired Competitive Programs; provided, further, that such Party shall cease all development and commercialization activities with respect to all such Acquired Competitive Products and Acquired Competitive Programs if such Party has not completed such divestiture within [***] after the closing of such acquisition (it being understood that such Party may thereafter continue its efforts to divest such asset);

(iii) During such divestiture period, the acquiring Party shall comply with Section 12.6 to separate its Development activities under this Agreement from its development activities relating to any Acquired Competitive Product or Acquired Competitive Program; and

(iv) Neither Party nor its Affiliates may acquire a Competitive Product or a Competitive Program on a standalone basis.

(b) If Ionis is the acquiring Party of an Acquired Competitive Product or Acquired Competitive Program, then during the Collaboration Divestiture Period until Ionis [***], Biogen may elect that [***].

(c) In addition, without limiting Section 12.5.3(a)(iv), if at any time during the Agreement Term, (i) Ionis acquires a Third Party or a portion of the business of a Third Party (whether by merger, stock purchase or purchase of assets) that is, prior to such acquisition, engaged (A) in [***] (an "***Associated Product***") or any Competitive Indication Collaboration Product, or (B) is engaged in [***] (an "***Associated Program***") or a Competitive Indication Collaboration Program, (ii) Ionis or an Ionis Affiliate [***] or (iii) Ionis or an Ionis Affiliate [***] then, in each case ((i) through (iii)) with respect to any Collaboration Program directed to the Collaboration Target to which the Associated Product, Associated Program, Competitive Collaboration Product or Competitive Collaboration Program is directed and with respect to any Collaboration Program intended for the same indication as the Competitive Indication Collaboration Product or the Competitive Indication Collaboration Program, Biogen may elect that [***] and Ionis shall comply with the same procedures as under Section 12.6 to separate its Development activities under this Agreement from its development activities relating to any such Associated Product, Associated Program, Competitive Collaboration Product, Competitive Collaboration Program, Competitive Indication Collaboration Product or Competitive Indication Collaboration Program.

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 Agreement 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 Agreement 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. **Protective Provisions.** At any time while (a) the Party involved in a Change of Control with a Competing Collaboration Acquirer or Competing Alternate Modality Acquirer, (b) the Party with an Acquired Competitive Product or Acquired Competitive Program or (c) Ionis (in cases where Ionis otherwise has an Associated Product, Associated Program, Competitive Product, Competitive Program, Competitive Indication Product or Competitive Indication Program) is conducting Development activities under this Agreement, then, in each case ((a) through (c)) such Party (as applicable under clause (a), (b) or (c)) must separate such Development activities from its or its Affiliates' other development activities relating to any such Competitive Collaboration Product, Competitive Collaboration Program, Directly Competitive Biogen Alternate Modality Product or Directly Competitive Biogen Alternate Modality Program and, in the case of Ionis, from any such Associated Product, Associated Program, Competitive Indication Product or Competitive Indication Program, as applicable (such other development activities, "***Competing Development Activities***"). To that end, and subject to the licenses granted to each Party (as applicable) under Section 4.3 or Section 4.4, any such Party will, and (if applicable) will cause the Competing Collaboration Acquirer or Competing Alternate Modality Acquirer to, (i) establish separate teams to conduct Development activities under this Agreement and such Competing Development Activities, (ii) prevent any Confidential Information relating to the Development, Manufacture or Commercialization of any applicable Product (including Know-How) from being disclosed to, or used by, individuals performing such Competing Development Activities and (iii) not use or reference in the development, manufacture or commercialization of the Competitive Collaboration Product or Directly Competitive Biogen Alternate Modality Product, any Know-How that is Confidential Information or conduct any activities Covered by any Patent Rights, in each case Controlled by the Party involved in the Change of Control or the acquisition or its Affiliates prior to the effective date of the Change of Control or the acquisition.

12.7. **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.

12.8. **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: Chief Legal Officer
E-mail: [***]

with a copy to:
Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199-3600
Attention: Mark Bellomy, Esq.
Email: mark.bellomy@ropesgray.com

or to such other address for such Party as it will have specified by like notice to the other Party; *provided* that notices of a change of address will be effective only upon receipt thereof. If delivered personally or by 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.

12.9. **Export Clause**. Each Party acknowledges that the Laws 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.

12.10. **Waiver**. Neither Party may waive or release any of its rights or interest 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.

12.11. **Severability**. If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, then 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.

12.12. **Entire Agreement**. This Agreement (together with the Schedules and Appendices hereto, including the ALS Letter Agreement), amends and restates the First Amended and Restated Agreement, is a comprehensive and integrated statement of the agreement between the Parties with respect to the subject matter hereof and fully supersedes the the First Amended and Restated Agreement for the period commencing on the Second 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.

12.13. **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.

12.14. **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, (h) unless otherwise specified, "$" is in reference to United States dollars and (i) 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.

12.15. **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.

12.16. **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.

12.17. **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.

12.18. **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.

12.19. **Counterparts**. This Agreement may be signed in counterparts, each of which will be deemed an original, notwithstanding variations in format or file designation that 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.

12.20. **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 Second Amendment Date.

BIOGEN MA INC.

By: */s/ Michael Ehlers*
Name: Michael Ehlers
Title: EVP, Research & Development

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/ Brett P. Monia*
Name: Brett P. Monia
Title: Chief Operating Officer/SVP Translational Medicine

List of Appendices and Schedules

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).

"***Acquired Competitive Product***" has the meaning set forth in Section 12.5.3(a).

"***Acquired Competitive Program***" has the meaning set forth in Section 12.5.3(a).

"***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.

"***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).

"***Associated Product***" has the meaning set forth in Section 12.5.3(c).

"***Associated Program***" has the meaning set forth in Section 12.5.3(c).

"***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 4.8.3.

"***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(c).

"***Biogen Reduced Participation and Information Obligations***" means solely with respect to the [***] (a) Biogen may [***], (b) Biogen will [***], (c) Biogen may [***] and (d) Biogen's obligation to [***], other than (i) reports required by Section 5.2.7, Section 6.14.1 and Section 10.4.4 (if applicable) (ii) upon Ionis' reasonable request, information to the extent required to confirm Biogen's compliance with its obligations under Section 5.1 and (iii) as reasonably required to permit Ionis to perform its obligations under this Agreement. The Biogen Reduced Participation and Information Obligations will not limit or diminish the scope of any licenses granted by Biogen to Ionis under this Agreement.

"***Biogen Reduced Royalty***" has the meaning set forth in Section 6.10.2(c).

"***Biogen Results***" has the meaning set forth in Section 4.8.3.

"***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 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 a Party, (a) a merger or consolidation of such Party with a Third Party which results in the voting securities of such Party 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 such Party's outstanding securities, (c) the sale or other transfer to a Third Party of all or substantially all of such Party's business to which the subject matter of this Agreement relates or (d) the stockholders or equity holders of such Party will approve a plan of complete liquidation of such Party or an agreement for the sale or disposition by such Party 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 12.5.3(a)(ii).

"***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(a). As of the Effective Date SOD-1 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(c).

"***Collaborator License***" has the meaning set forth in Section 7.1.3(c).

"***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 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 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.

"***Competing Development Activities***" has the meaning set forth in Section 12.6.

"***Competitive Indication Product***" means any product intended for use in the same indication as any Development Candidate or Collaboration Product.

"***Competitive Indication Program***" means any internal research program for which a budget has been established or to which research personnel have been assigned, with the goal of discovering and developing a Competitive Indication Product for which drug discovery activities have been initiated.

"***Competitive Infringement***" has the meaning set forth in Section 7.5.1.

"***Competitive Collaboration Product***" means any Oligonucleotide that is designed to bind to or directly modulate the RNA that encodes a High Interest Target or Collaboration Target, other than a Collaboration Product that is being pursued under this Agreement.

"***Competitive Collaboration Program***" means any internal research program for which a budget has been established or to which research personnel have been assigned, with the goal of discovering and developing a Competitive Collaboration Product for which drug discovery activities have been initiated.

"***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 any 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(d).

"***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 applicable Third Party Compensation. Notwithstanding anything to the contrary under this Agreement, with respect to any Third Party acquirer of a Party that becomes an Affiliate of a Party after the Effective Date, no intellectual property of such Third Party acquirer 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 4.4.

"***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 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 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 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, other than a Biogen Alternate Modality Product that is being pursued under this Agreement.

"***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.

"***Enabled Core Program Patents***" means Program Patents Controlled by a Party or any of its Affiliates on the Effective Date or during the Agreement Term claiming (a) methods of dosing (frequency, duration, concentration, volume, etc.) generally applicable to Oligonucleotides to achieve optimal tissue distribution or enhance other properties of an Oligonucleotide; (b) methods of determining an effective human dose based on animal data that are generally applicable to Oligonucleotides; (c) methods of determining an effective dose based on actual or modeled pharmacokinetic data generally applicable to Oligonucleotides; (d) methods of identifying or optimizing predictive biomarkers for diseases; (e) observations about a disease based on data from a natural history study; (f) proprietary disease models; or (g) methods of using radio-labeled ligands with Oligonucleotides in animals.

"***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, any prophylactic or therapeutic use or form of administration 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 Amended and Restated Agreement***" has the meaning set forth in the Preamble of this Agreement.

"***First Amendment Date***" has the meaning set forth in the Preamble of 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 the License Effective Date for the applicable Collaboration Program.

"***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 4.8.2(c) fairly applied and as employed on a consistent basis throughout Ionis' operations.

"***GAAP***" means generally accepted accounting principles in the United States, consistently applied.

"***Gene-Editing Product***" means an Oligonucleotide 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 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, (iii) the Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated December 10, 2012, (iv) the Research Collaboration, Option and License Agreement between the Parties dated December 19, 2017 and (v) the Neurology III Agreement, 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 4.8.3.

"***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.

"***License Effective Date***" means, on an Option-by-Option and Program-by-Program basis, the date on which Biogen notifies Ionis in writing that it wishes to exercise the Option and pays to Ionis the applicable license fee set forth in Section 6.6 (in the event Biogen wishes to exercise its Option for a Collaboration Program) or Section 6.2.2 (in the event Biogen wishes to exercise its Option for a Biogen Alternate Modality Program) for such Program.

"***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 Program-by- Program 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 4.3.1(a), Section 4.3.2, Section 4.4, Section 4.5, Section 4.7.2 and Section 4.8.3 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 Product-Specific Patent***" has the meaning set forth in Section 7.2.4.

"***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 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 III Agreement***" means that certain New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Parties dated April 19, 2018, as amended or restated from time to time.

"***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.

"***NPV***" has the meaning set forth in Appendix 3.

"***[***]***" means diseases that have, as their [***].

"***Oligonucleotide***" means a synthetic compound that comprises or consists of at least 5 linked nucleosides (including any analog, variant, mimic, or mimetic thereof). For clarity, the [***] of Oligonucleotides [***]. Oligonucleotides [***]. Oligonucleotides may be single-stranded or multi-stranded.

"***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 as a Collaboration Program hereunder and ending on the License Effective Date or 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 Collaboration Product***" has the meaning set forth in Section 12.5.2.

"***Pre-Existing Competitive Collaboration Program***" 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, 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 (a) the specific composition of matter of such Product, (b) methods of using such Product as a prophylactic or therapeutic or (c) the specific method of manufacture of such Product (unless in the case of (c), such Patent Rights also claim any other product or services of Ionis); *provided however*, Patent Rights Controlled by Ionis or any of its Affiliates that (i) include claims that are directed to subject matter applicable to ASOs or products in general, or (ii) 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 (i) and (ii), such Patent Rights will be considered Ionis Core Technology Patents.

"***Program***" has the meaning set forth in Section 7.2.2.

"***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 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 4.8.3.

"***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).

"***Second Amendment Date***" has the meaning set forth in the Preamble of this Agreement.

"***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(d).

"***Target Related Biogen Program Claim***" has the meaning set forth in Section 4.3.4.

"***Target Related Ionis Program Claim***" has the meaning set forth in Section 4.3.2.

"***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 (a) 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 (b) 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 (a) above with respect to such application issues.

APPENDIX 2

Development Candidate Checklist

[***]

APPENDIX 3

Multi-Indication Target Process

Neurology Targets with Broader Therapeutic Benefit.

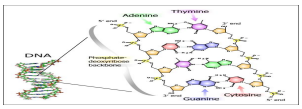
(a) If, pursuant to Section 1.2.3(d), the CSC is unable to agree upon whether a Multi-Indication Target is a Primarily Neuro Multi-Indication Target, Equal Multi-Indication Target or Primarily Other Multi-Indication Target, the Parties will engage an expert panel under Section 12.1.4 to make such determination. 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
E-mail: [***]

Re: Establishment of Cost Estimates and Milestone Payments

Dear [*Chief Operating Officer*]:

Reference is hereby made to that certain Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between Ionis and Biogen dated _____ ___, [2018] (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,

[*VP of Corporate Development*]
Vice President, Corporate Development
Biogen MA Inc.

CONFIRMED ON BEHALF OF IONIS PHARMACEUTICALS, INC.:

By: _____

Name: _____

Title: _____

Date: _____

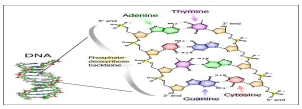
Cc: Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
E-mail: [***]

Exhibit A

Collaboration Program: _____

Development Candidate: _____

[***]



[*Date*]

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Operating Officer
E-mail: [***]

Re: Establishment of Biogen-Approved Costs

Dear [*Chief Operating Officer*]:

Reference is hereby made to that certain Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between Ionis and Biogen dated _____ ___, 2018 (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,

[*VP of Corporate Development*]
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
E-mail: [***]

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. SOD-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 [***] 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 30 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, Senior Strategic Advisor

Frank Bennett, SVP, Head of Research

Richard Geary, SVP, Head of Development

Biogen

Michael Ehlers, EVP, Research and Development

Katherine Dawson, VP, Late Stage Clinical Development

Anabella Villalobos, SVP, Biotherapeutic and Medicinal Sciences

Daniel Karp, EVP Corporate 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 Neurology JRC as outlined in Section 1.11.

SCHEDULE 4.3.1(a)

Drug Substance Process and Formulation Development Activities

[***]

SCHEDULE 4.8.2(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

[***]

[***]	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**	**[***]**
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[***]

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

	[***]	[***]	[***]	[***]	[***]
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SCHEDULE 8.2.4(b)

Ionis Manufacturing and Analytical Patents

[***]	[***]	[***]	[***]	[***]	[***]
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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

[***]	[***]	[***]
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Schedule 12.5

Table B
Applicable [***] under Section 12.5.1(b) in Change of Control

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Exhibit 10.69

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)(4), 240.24B-2

AMENDMENT NO. 1

This Amendment No. 1 (the "Amendment") to the Strategic Collaboration Agreement dated July 31st, 2015 (the "Agreement"), is made by and between

(1) ASTRAZENECA AB, a company incorporated in Sweden under no. 556011-7482 with its registered office at SE-151 85 Södertälje, Sweden ("AstraZeneca") and

(2) IONIS PHARMACEUTICALS, INC., a Delaware corporation, (formally known as Isis Pharmaceuticals, Inc.) having its principal place of business at 2855 Gazelle Court, Carlsbad, California 92010 ("Ionis"),

and is made effective as of October 18th, 2018 (the "Amendment Effective Date").

Recitals

WHEREAS, the Parties desire to further amend and restate certain terms and conditions of the Agreement.

Agreement

NOW, THEREFORE, in consideration of the mutual covenants contained in this Amendment, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, agree as follows:

1. **Definitions**

Any capitalized term not separately defined in this Amendment shall have the meaning ascribed to it in the Agreement.

2. **Modifications**

Section 5.1.2. of the Agreement is hereby deleted in its entirety and replaced by the following:

"5.1.2. **Integrated Product Plans**. For each Licensed Program, AstraZeneca will prepare a global integrated Product plan or a comparable document consistent with AstraZeneca's then current internal practices for AstraZeneca's internal programs outlining key aspects of the Development of the Product being Developed from such Program through all Approvals as well as, as Development proceeds and when such information is available, key aspects of worldwide regulatory strategy, pricing and market access strategy, market launch, and Commercialization (each plan or other such document, an "Integrated Product Plan" or "IPP"). On a Product-by-Product basis, AstraZeneca will prepare each IPP no later than [***] for the relevant Product, and the IPP will contain high level information consistent with AstraZeneca's development and commercialization plans for its similar products at similar stages of development and commercialization in the same AstraZeneca franchise, including without limitation a status update, timelines, goals, and the criteria AstraZeneca will use to make internal decisions, but excluding information that AstraZeneca is required not to share even under confidentiality pursuant to restrictions imposed by any Third Party. Once AstraZeneca has prepared an IPP, AstraZeneca will update it consistent with AstraZeneca's standard practice (including if the IPP is updated and presented to an AstraZeneca internal committee) but at least Annually and will provide such updates to Ionis. AstraZeneca and Ionis will meet (through the JSC or as the Parties may otherwise agree) on a yearly basis to discuss the draft of the IPP and AstraZeneca will consider, in good faith, any proposals and comments made by Ionis or incorporation in the IPP. AstraZeneca and Ionis will [***], to discuss the status of execution of the IPP. Additionally, subject to AstraZeneca's confidentiality obligations to any Third Party, AstraZeneca may provide more frequent updates in the case of extraordinary material events (e.g. approvals, regulatory feedback, etc.) as deemed appropriate by AstraZeneca. For the avoidance of doubt, information provided by AstraZeneca to Ionis pursuant to this Section 5.1.2 shall be treated by Ionis as AstraZeneca's Confidential Information subject to the provisions in Article 11."

3. **Amendment Effective Date**

This Amendment shall become effective on the Amendment Effective Date.

4. **Entire Agreement**

This Amendment, together with the Agreement, constitutes the entire agreement between the Parties with respect to the subject matter of the Agreement. The Agreement together with this Amendment supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreement, as amended. Each Party confirms that it is not relying on any representations, warranties, or covenants of the Party except as specifically set out in the Agreement as amended. Nothing in this Amendment is intended to limit or exclude any liability or fraud. The Parties hereby agree that subject to the modifications specifically stated in this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect.

5. **Execution**

THIS AMENDMENT IS EXECUTED by the authorized representatives of the parties as of the date first written above.

ASTRAZENECA AB (publ.)		**IONIS PHARMACEUTICALS, INC.**	
Signature:	/s/ *Regina Fritsche Danielson*	Signature:	/s/ *Brett Monia*
Name:	Regina Fritsche Danielson	Name:	Brett Monia
Title:	VP and Head of IMED CVRM	Title:	Chief Operating Officer

Exhibit 10.70

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)(4), 240.24B-2

AMENDMENT NO. 4

This Amendment No. 4 (the "Amendment") to the Collaboration, License and Development Agreement dated December 7th, 2012 (the "Agreement"), is made by and between

(1) ASTRAZENECA AB, a company incorporated in Sweden under no. 556011-7482 with its registered office at SE-151 85 Södertälje, Sweden ("AstraZeneca") and

(2) IONIS PHARMACEUTICALS, INC., a Delaware corporation, (formally known as Isis Pharmaceuticals, Inc.) having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("Ionis"),

and is made effective as of October 18th, 2018 (the "Amendment Effective Date").

Recitals

WHEREAS, the Parties desire to further amend and restate certain terms and conditions of the Agreement.

Agreement

NOW, THEREFORE, in consideration of the mutual covenants contained in this Amendment, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, agree as follows:

1. **Definitions**

Any capitalized term not separately defined in this Amendment shall have the meaning ascribed to it in the Agreement.

2. **Modifications**

Section 7.1.1 of the Agreement is hereby deleted in its entirety and replaced by the following:

"7.1.1. **Integrated Product Plans**. AstraZeneca will prepare a Development and global integrated Product plan or a comparable document consistent with AstraZeneca's then current internal practices for AstraZeneca's internal programs outlining key aspects of the Development of each Product licensed by AstraZeneca under Section 6.1.1, Section 6.1.2 and Section 6.1.3 through all Approvals as well as, as Development proceeds and when such information is available, key aspects of worldwide regulatory strategy, pricing and market access strategy, market launch, and Commercialization (each plan or other such document, an "Integrated Development Plan" or "IDP"). On a Product-by-Product basis, for each Product licensed by AstraZeneca under Section 6.1.1, Section 6.1.2 or Section 6.1.3, as the case may be, AstraZeneca will prepare each IDP no later than [***] for such Product, and the IDP will contain high level information consistent with AstraZeneca's development and commercialization plans for its similar products at similar stages of development and commercialization in the same AstraZeneca franchise, including material updates, timelines, goals, and the criteria AstraZeneca will use to make internal decisions relating to the Product, provided however that it will be at AstraZeneca's sole discretion whether to and in what format to provide any information which (i) AstraZeneca is required not to share even under confidentiality pursuant to restrictions imposed by any Third Party, or (ii) contains AstraZeneca Confidential Information regarding the use of AstraZeneca's other portfolio compounds used alone or in combination with other AstraZeneca or Third Party products. Once AstraZeneca has prepared an IDP, AstraZeneca will update it consistent with AstraZeneca's standard practice (including if the IDP is updated and presented to an AstraZeneca internal committee) but at least Annually and will provide such updates to Ionis. AstraZeneca and Ionis will meet (through the JSC or as the Parties may otherwise agree) on a yearly basis to discuss the draft of the IDP and AstraZeneca will consider, in good faith, any proposals and comments made by Ionis for incorporation in the final IDP. AstraZeneca and Ionis will [***], to discuss the status of execution of the IDP. Additionally, subject to any restrictions imposed by any Third Party, AstraZeneca may provide more frequent updates in the case of extraordinary material events (e.g. approvals, regulatory feedback, etc.) as deemed appropriate by AstraZeneca. For the avoidance of doubt, information provided by AstraZeneca to Ionis pursuant to this Section 7.1.1 shall be treated by Ionis as AstraZeneca's Confidential Information subject to the provisions in Article 13. Notwithstanding the foregoing, on a Gene Target-by-Gene Target basis, AstraZeneca's obligations to provide Ionis with information or reports under this Section 7.1.1 will terminate if Ionis independently or for or with an Affiliate or Third Party engages in any activity to discover, research or develop an ASO designed to bind to the RNA that encodes such Gene Target in the Field other than in the course of performing its obligations under, or to the extent permitted by, this Agreement."

3. **Amendment Effective Date**

This Amendment shall become effective on the Amendment Effective Date.

4. **Entire Agreement**

This Amendment, together with the Agreement, constitutes the entire agreement between the Parties with respect to the subject matter of the Agreement. The Agreement together with this Amendment and any prior Amendments thereto supersedes all prior agreements, whether written or oral, with respect to the subject matter of the Agreement, as amended. Each Party confirms that it is not relying on any representations, warranties, or covenants of the Party except as specifically set out in the Agreement as amended. Nothing in this Amendment is intended to limit or exclude any liability or fraud. The Parties hereby agree that subject to the modifications specifically stated in this Amendment, all other terms and conditions of the Agreement shall remain in full force and effect.

5. **Execution**

THIS AMENDMENT IS EXECUTED by the authorized representatives of the Parties as of the date first written above.

ASTRAZENECA AB (publ.)		**IONIS PHARMACEUTICALS, INC.**	
Signature:	/s/ *Regina Fritsche Danielson*	Signature:	/s/ *Brett Monia*
Name:	Regina Fritsche Danielson	Name:	Brett Monia
Title:	VP and Head of IMED CVRM	Title:	Chief Operating Officer

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Subsidiaries of Ionis Pharmaceuticals, Inc:

Ionis USA Limited, a United Kingdom Limited Private Company

Osprey Therapeutics, Inc., a Delaware Corporation

PerIsis I Development Corporation, a Delaware Corporation

Symphony GenIsis, Inc., a Delaware Corporation

Ionis Development (Ireland) Limited, an Ireland Limited Private Company

Akcea Therapeutics, Inc., a Delaware Corporation

Subsidiaries of Akcea Therapeutics, Inc.:

Akcea Therapeutics Canada Inc., a Canadian Corporation

Akcea Therapeutics France SAS, a French Company

Akcea Therapeutics Germany GmbH, a German Corporation

Akcea Therapeutics UK Limited, a United Kingdom Limited Private Company

Akcea Securities Corporation., a Massachusetts Corporation

Akcea Therapeutics Ireland Limited, an Ireland Limited Private Company

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statement on Form S-3 (No. 333-217422) and in the related Prospectuses, as applicable, and in the Registration Statements on Form S-8 (Nos. 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777, 333-151996, 333-160269, 333-168674, 333-176136, 333-184788, 333-190408, 333-207900, and 333-219801) of Ionis Pharmaceuticals, Inc. of our reports dated March 1, 2019, 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) of Ionis Pharmaceuticals, Inc. for the year ended December 31, 2018.

/s/ ERNST & YOUNG LLP

San Diego, California
March 1, 2019

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: March 1, 2019

/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: March 1, 2019

/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, 2018, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: March 1, 2019

/s/ STANLEY T. CROOKE
Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

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

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

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